University of Alberta

Novel Domino Nazarov Cyclization/Azide Trapping Process

by

Ali Rostami ©

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ABSTRACT

Tandem or domino reactions are gaining a great deal of attention within the field of organic synthesis. The capability of the formation of multiple new bonds or rings in a single stereoselective operation often leads to a great increase in molecular complexity, which can reduce the number of chemical steps overall with in a synthesis.

We have developed a novel domino reaction, Nazarov electrocyclization/azide trapping process, which allows for the formation of complex heterocyclic systems. This reaction involves capture of the oxyallyl intermediate of the Nazarov reaction with an alkyl azide *via* an inter- or an intramolecular process to furnish various functionalized mono- and polycyclic lactams. In this process, one new carbon-carbon bond, two new carbon-nitrogen bonds and up to three stereogenic centers can be formed in one synthetic step. This methodology demonstrates rapid access to nitrogen heterocycles bearing indolizidinone or *N*-alkylated piperidinone structural motifs.

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Dedicated to my lovely parents, Parvaneh and Abbas

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LIST OF ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Anal.	Elemental analysis
app.	Apparent
APT	Attached proton test
aq	Aqueous
Ar	Aryl
Bn	Benzyl
brs	Broad singlet
Bu	Butyl
Calcd.	Calculated
COSY	Homonuclear correlation spectroscopy
conc.	Concentrated
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dddd	Doublet of doublets of doublets of doublets
dq	Doublet of quartets
DCM	Dichloromethane
DIAD	Di*iso*propyl azodicarboxylate

DMAP	4-(*N,N*)-Dimethylamino pyridine
DMP	Dess-Martin periodinane
DPPA	Diphenyl phosphoryl azide
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
FTIR	Fourier-transform infrared
hr.	hour/hours
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
IR	Infrared
LA	Lewis acid
LC-MS	Liquid chromatography-mass spectrometry
m	Multiplet
Me	Methyl
mg	Milligrams
min	Minute/minutes
mL	Milliliters
mmol	Millimoles
m.p.	Melting point

MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ph	phenyl
ppm	Parts per million
Py	Pyridine
q	quartet
qd	quartet of doublets
R	Generic alkyl group
R_f	Retention factor (in chromatography)
rt	Room temperature
s	Singlet
t	Triplet
tt	Triplet of triplets
td	Triplet of doublets
ttd	Triplet of triplets of doublets
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*t*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol

1 CHAPTER 1

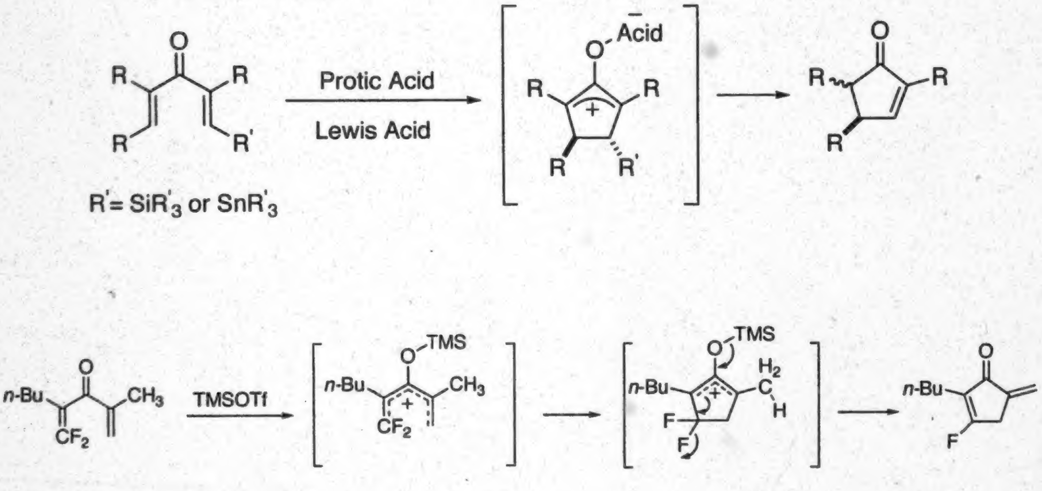
1.1 The Interrupted Nazarov Reaction

1.2 Introduction

Mirroring nature's complexity with greater efficiency, organic synthesis has become a valuable technique for the construction of complex molecules. Consequently, tandem or "domino" processes are especially attractive methods in this field.[1] These reactions typically consist of the formation of multiple new bonds or rings in a single stereoselective operation generating complex polycyclic systems. The interrupted Nazarov reaction is one of these useful processes. It includes an initial electrocyclization reaction to form a new carbon-carbon bond and a valuable cyclopentanoid ring, while producing a reactive oxyallyl intermediate. This oxyallyl intermediate could be trapped in either inter- or intramolecular fashion to produce elaborate molecules. In this chapter, numerous examples of this process will be reviewed and analyzed.

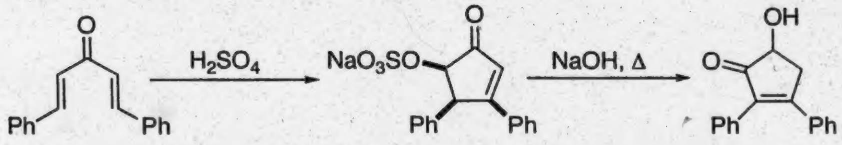
1.3 Nazarov Cyclization

The Nazarov cyclization is an interesting approach for cyclopentannulation.[2] In 1903, the Nazarov reaction was reported,[3] investigated and fully accessed by Nazarov and his co-workers.[4] A well defined pericyclic mechanism has been reported based on experimental and theoretical studies.[5] Treating a simple dienone with a protic or Lewis acid leads to a 4π-electron conrotatory ring closure to provide the five-membered cyclic oxyallyl intermediate. Proton elimination and protonation of the transient enolate establishes cyclopentenones with up to two new stereocenters. It has been shown that the presence of electron-donating substituents at the α-positions of the dienone increases the rate of the electrocyclization.[5] Directed Nazarov reactions could be achieved by the proper substitution of a heteroatom, silicon, tin or fluorine on the dienone precursors. These substituents have an impact on the regiochemical outcome of the reaction (the position of the cyclopentenone double bond) by controlling the termination step (Scheme 1.1).[6]



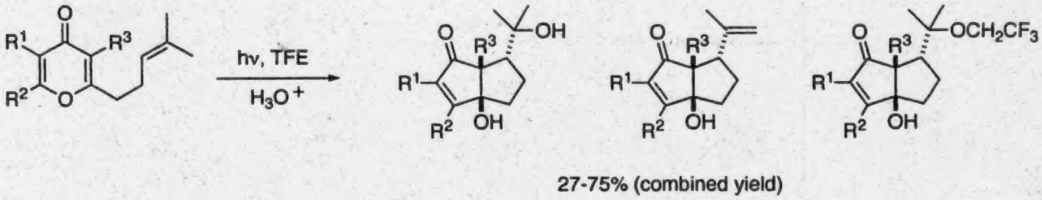
Scheme 1.1.1 Directed Nazarov Reaction

One of the first examples of the interrupted Nazarov reaction involved solvent capture of the resultant oxyallyl intermediate. Treating acyclic divinyl ketones with sulfuric acid provides sulfate capture of the Nazarov oxyallyl intermediate (Scheme 1.2).[7]



Scheme 1.2 Solvent Capture of the Nazarov Intermediate

Upon irradiation, pyran-4-ones bearing a pendant olefin or arene nucleophiles undergo nucleophilic trapping of the oxyallyl intermediates to furnish diquinanes and hydrindanes (Scheme 1.3).[8] While forming complex polycyclic systems, there were some limitations associated with this process. Although the angular hydroxyl group in the products could have been useful for Grob fragmentation, it was not particularly appealing due to undesirable reactions.[9] Also, the costly trifluoroethanol used as a protic solvent led to economic concerns and was thus not a preferred solvent in the development of asymmetric reactions. Also, scale-up was limited for photochemical reactions.



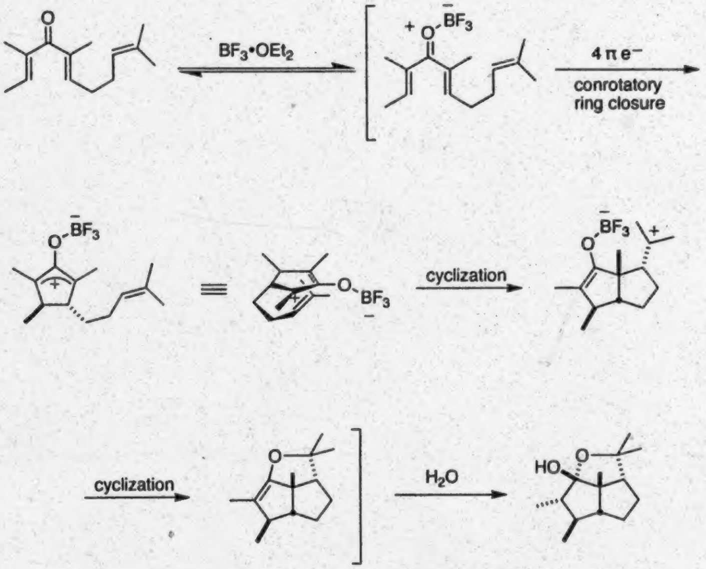
Scheme 1.3 Nucleophilic Trapping of the Photochemically Generated Oxyallyl Carbocation

The Nazarov cyclization proceeds via oxyallyl intermediates resembling those generated photochemically from pyran-4-ones. The interrupted Nazarov reaction provides many advantages over the classical Nazarov reaction. In the classical Nazarov reaction, the terminal elimination step demolishes a stereocenter formed during the cyclization, which could otherwise be prevented by the trapping of the oxyallyl cation. Moreover, the Lewis acid-mediated processes have opened the doors for the asymmetric variant of this cyclization using chelation control or chiral Lewis acids.[10]

1.4 Intramolecular Interrupted Nazarov Cyclization

1.4.1 Cycloisomerization of Acyclic Trienone

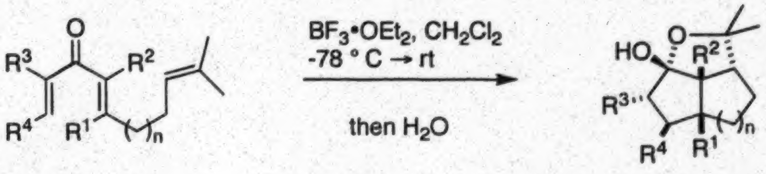
One of the earliest examples of the interrupted Nazarov cyclization relied on the trapping of the Nazarov oxyallyl intermediate *via* cationic cyclization onto pendant olefins. In this single chemical step, acyclic, achiral trienones were converted into diquinanes with the formation of two new carbon-carbon bonds and up to five new stereocenters.[11]



Scheme 1.4 Cycloisomerization of Acyclic Trienone

These cyclizations proceed as follows: First, the Lewis acid complexes to the carbonyl moiety of the dienone to initiate the expected four-electron conrotatory electrocyclization process. Next, the oxyallyl cation generated in the course of the reaction is trapped by the pendant olefin in a 5-exo fashion to generate the tertiary carbocation. The rationale for the final ring closure would be based on the endo-disposed geometry of the generated tertiary carbocation through a compact transition state. The hemiketal product was formed after the hydration of the strained enol ether via the selective protonation from the convex face (Scheme 1.4).

Table 1.1 Olefin Trapping of the Nazarov Intermediate



1.1 **1.2**

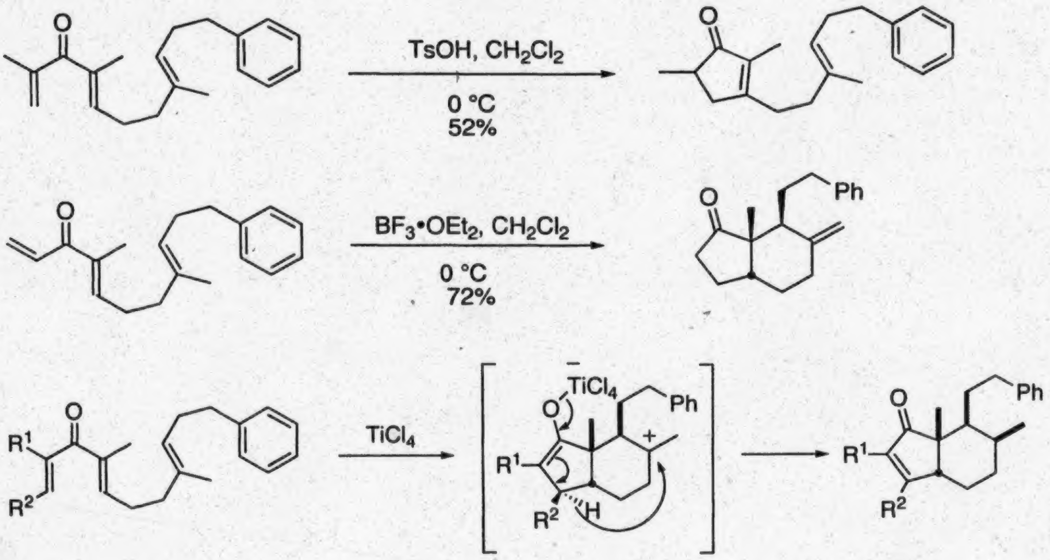
entry	dienone	R¹	R²	R³	R⁴	n	product	yield (%)[a]
1	**1.1a**	H	CH_3	CH_3	H	1	**1.2a**	75
2	**1.1b**	H	CH_3	$C(CH_3)_3$	H	1	**1.2b**	89
3	**1.1c**	H	CH_3	CH_2CH_3	CH_3	1	**1.2c**	73
4	**1.1d**	H	CH_3	-$(CH_2)_4$-		1	**1.2d**	62
5	**1.1e**	H	CH_3	CH_3	H	2	**1.2e**	42
6	**1.1f**	CH_3	H	CH_3	H	1	**1.2f**	--[b]

(a) Isolated yield. (b) Complex mixture of products.

Those substrates lacking α-substitution showed resistance to cyclization. In the case where R^2=R^4=H and R^3=R^1=Me, multiple unidentified products were obtained (Table 1.1). There are two contributing factors to these low yields: First, these substrates would likely exist in the undesirable "W" conformation versus the "U"-shaped conformation necessary for the Nazarov cyclization to occur. Second, there would be a decrease in the potential for cation-olefin cyclization because of the greater charge density on the more distant substituted carbon of the oxyallyl system.

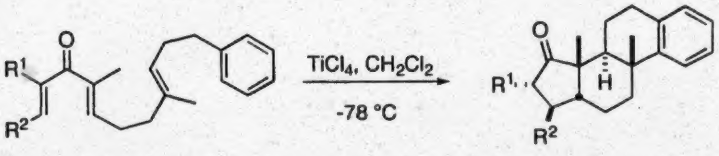
1.4.2 Cascade Cyclization

The elegant work of West and Bender has demonstrated the significance of domino reactions in cationic olefin polycyclizations.[12] In this cascade polycyclization process, the oxyallyl unit and a terminal aryl unit have been separated by a pendant alkene group. This specific method leads to the production of tetra- or pentacyclic structures with up to six stereocenters with complete diastereoselectivity from simple achiral trienones. Initially, treatment of the trienone with protic acid led to the "traditional" Nazarov cyclization product (Scheme 1.5), while in the presence of $BF_3 \bullet OEt_2$, hydrindenone was furnished. The formation of the desired cascade cyclization product was prevented by the formation of an elimination product (Scheme 1.5). Finally, treatment of the trienone with $TiCl_4$ at -78 °C cleanly furnished the cascade polycyclization product with no mixture of elimination products (Table 1.2). The formation of minor products in the case of **1.3c** and **1.3e** is believed to have been caused by an intramolecular hydride transfer process (Scheme 1.5).


O
TsOH, CH_2Cl_2
0 °C
52%
O
O
BF_3•OEt_2, CH_2Cl_2
0 °C
72%
O
Ph
R^1
O
R^2
$TiCl_4$
$TiCl_4$
O
Ph
R^1
+
R^2
H
O
Ph
R^1
R^2

Scheme 1.5 Cascade Cyclization

Table 1.2 Cascade Cycloisomerization


R^1
O
R^2
$TiCl_4$, CH_2Cl_2
-78 °C
O
R^1
H
R^2

1.3

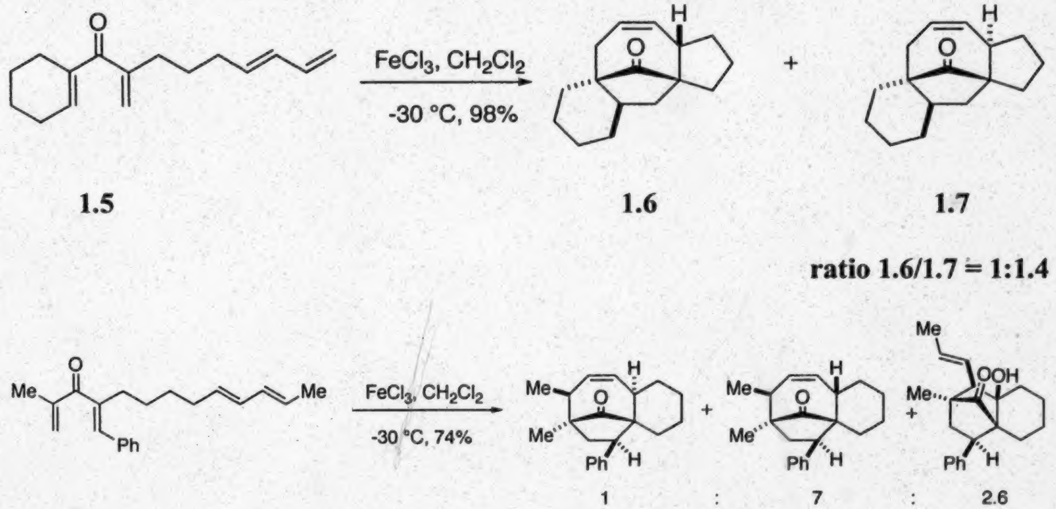
1.4

entry	substrate	R^1	R^2	product	yield (%)[a]
1	**1.3a**	H	H	**1.4a**	--[b]
2	**1.3b**	Me	H	**1.4b**	99
3	**1.3c**	Me	Et	**1.4c**	73
4	**1.3d**	-$(CH_2)_4$-		**1.4d**	98
5	**1.3e**	-$(CH_2)_5$-		**1.4e**	74

(a) Isolated yield. (b) Oligomeric products were isolated.

1.4.3 [4+3] Cycloaddition

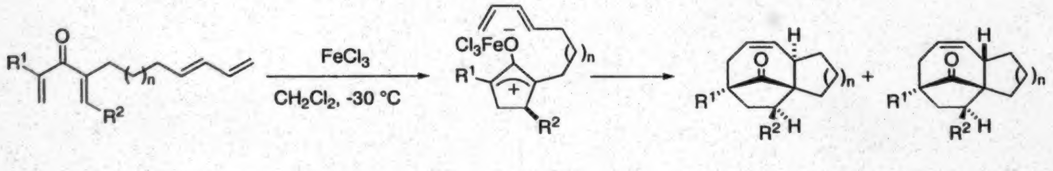
[4+3]-cycloadditions utilizing 1,3-dienes and an oxyallyl unit are particularly efficient methods for the construction of seven-membered carbocycles bearing useful functional groups. One of these methods has been reported by Wang and West,[13] through which a 1,4-diene-3-one bearing a pendant 1,3-diene undergoes "domino" Nazarov cyclization followed by an intramolecular [4+3]-cycloaddition to provide distinctive tricyclic compounds. Throughout this process, acyclic, achiral substrates were converted to tri- and tetracyclic products in moderate to excellent yields with concomitant formation of three new carbon-carbon bonds and up to five new stereocenters (Scheme 1.6).[14]



Scheme 1.6 Intramolecular [4+3] Cycloaddition

In an example containing an extra methyl substituent on the 1,3-diene, the electrocyclization/[4+3]-cycloaddition led to three products in a combined yield of 74%. The *exo* cycloadduct was the major product, and the formal [3+2] adduct was also obtained. The rationale behind the formation of this novel product relies on stepwise nucleophilic trapping of the oxyallyl cation, followed by enolate closure onto the resulting allylic carbocation (Scheme 1.6).

Table 1.3 Intramolecular [4+3] Cycloaddition

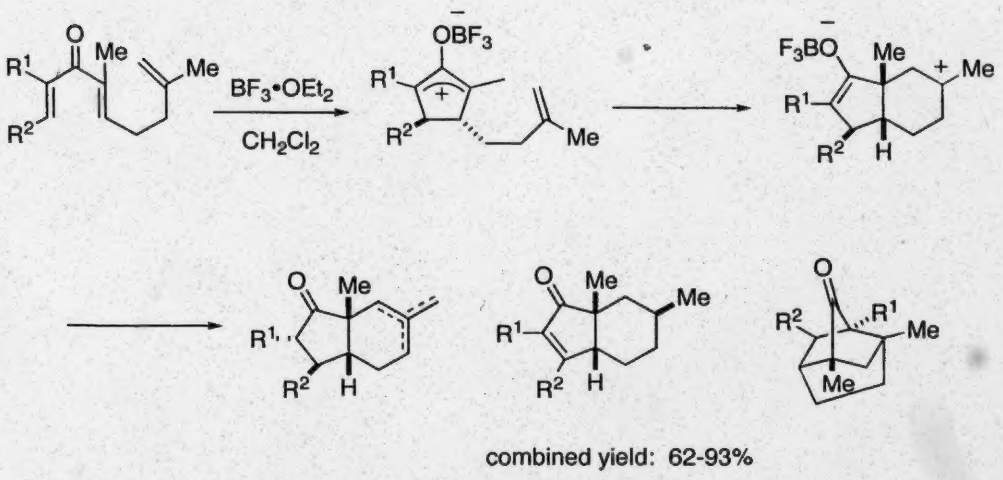


1.8 **1.9** **1.10**

entry	substrate	R^1	R^2	n	yield	ratio 1.9:1.10
1	**1.8a**	CH_3	CH_3	1	65	1.3:1
2	**1.8b**	CH_3	CH_3	1	72	1.3:1
3	**1.8c**	CH_3	Ph	2	67	1:0
4	**1.8d**	CH_3	Ph	2	75	1:0

1.4.4 6-*Endo* Trapping of the Nazarov Oxyallyl Intermediate

Not only can the oxyallyl carbocation be intercepted via 5- or 6-*exo* cation-olefin cyclization, producing diquinane products, but it can also undergo 6-*endo* cyclization to generate carbocationic hydrindane intermediates. These intermediates can undergo a variety of termination steps (Scheme 1.7).[15] Treating different trienones, bearing various substituents, with $BF_3 \bullet OEt_2$ at -78 °C, followed by warming to 0 °C and workup, led to three unique products, all containing the hydrindane skeleton (Scheme 1.7).

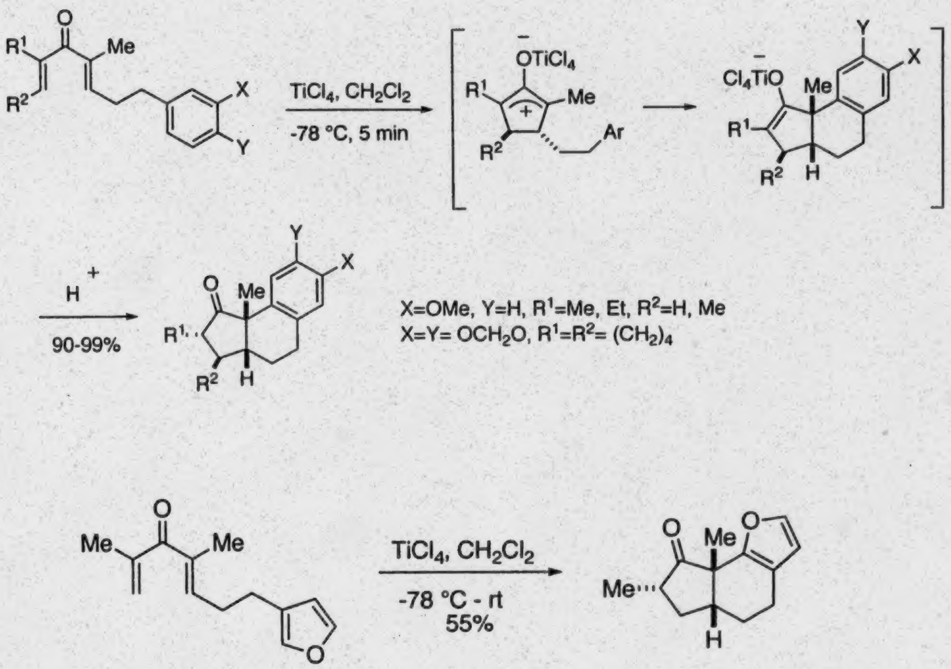


Scheme 1.7 6-*Endo* Trapping of the Nazarov Oxyallyl Intermediate

These compounds presumably arose from a common intermediate generated from Nazarov electrocyclization and subsequent 6-endo ring closure. The reactive intermediate, which contains both a tertiary carbocation and a boron enolate could undergo an array of diverse termination pathways. Hydrindenone regioisomers were obtained from carbocation elimination with simultaneous enolate quenching. Tricyclic products were formed *via* a formal [3+2] cycloaddition of the oxyallyl carbocation with the pendant alkene. Formation of the bicyclic enone was the result of an intramolecular hydride transfer.

1.4.5 Arene Trapping of the Nazarov Intermediate

In 2001, West and coworkers[16] reported a novel route for the construction of benzohydrindane ring skeletons. This methodology converted aryl dienones to benzohydrindenones *via* a "domino" Nazarov cyclization followed by an electrophilic aromatic substitution. The unsubstituted phenyl was used with $BF_3•OEt_2$ and $TiCl_4$ as Lewis acids in the primary attempts. In these experiments, no trapping products were obtained, ostensibly due to the low nucleophilicity of the phenyl group. When more electron-rich arenes were used in the presence of $TiCl_4$ as a Lewis acid, the arene-fused hydrindenones were found to have been formed cleanly (Scheme 1.8). This particular methodology has been used to assemble a furan moiety on to the hydrindenone skeleton (Scheme 1.8).

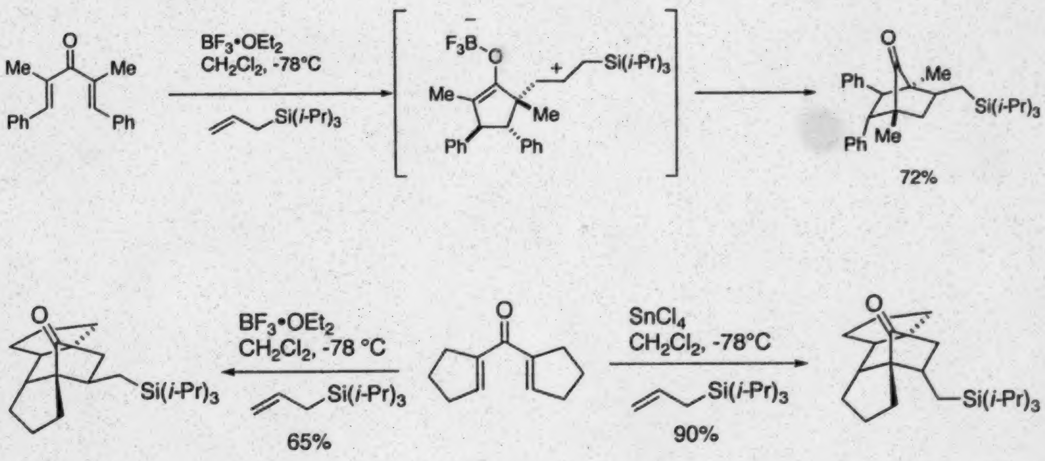

O
R¹
R²
Me
X
Y
TiCl₄, CH₂Cl₂
-78 °C, 5 min
OTiCl₄
R¹
Me
+
R²
Ar
Cl₄TiO
Me
Y
X
R¹
R²
H
H⁺
90-99%
O
Me
Y
X
R¹
R²
H
X=OMe, Y=H, R¹=Me, Et, R²=H, Me
X=Y= OCH₂O, R¹=R²= (CH₂)₄
O
Me
Me
O
TiCl₄, CH₂Cl₂
-78 °C - rt
55%
O
Me
O
Me
H

Scheme 1.8 Arene Trapping of the Nazarov Intermediate

1.5 Intermolecular Trapping of the Oxyallyl Intermediate

1.5.1 Domino Electrocyclization/[3+2] Cycloadditions with Allylsilanes

As previously discussed, many polycyclic compounds have been produced by the intramolecular trapping of oxyallyl cations formed during the Nazarov cyclization of different dienones. Giese and West have shown that the oxyallyl cation, which is generated during Nazarov cyclization, could also be intercepted in an intermolecular fashion with electron rich trapping reagents.[17] The oxyallyl carbocation in this methodology reacted with allylsilane in a formal [3+2] fashion to generate bicyclo[2.2.1]heptanones as the major product along with allylated compounds as minor products. These bridged bicyclic systems have been formed from two simple, unsaturated units in this process (Scheme 1.9) .



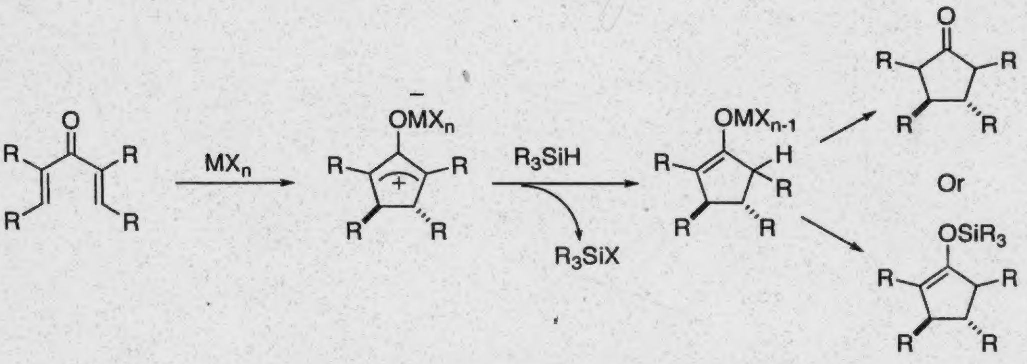
O
Me
Me
Ph
Ph
BF_3•OEt_2
CH_2Cl_2, -78°C
Si(i-Pr)$_3$
F_3B
O
+
Si(i-Pr)$_3$
Me
Me
Ph
Ph
O
Ph
Me
Si(i-Pr)$_3$
Ph
Me
72%
O
Si(i-Pr)$_3$
BF_3•OEt_2
CH_2Cl_2, -78 °C
Si(i-Pr)$_3$
65%
O
SnCl$_4$
CH_2Cl_2, -78°C
Si(i-Pr)$_3$
90%
O
Si(i-Pr)$_3$

Scheme 1.9 Domino Electrocyclization/[3+2] Cycloadditions with Allylsilanes

The formation of these bicyclic compounds involves three consecutive processes: a) electrocyclic closure of the dienone mediated by Lewis acid to generate the oxyallyl intermediate; b) nucleophilic attack of the γ-carbon atom of the allyl silane at one of the oxyallyl ends to generate an intermediate with a boron enolate and a silicon-stabilized carbocation; and c) capturing of the carbocation by the Lewis acid enolate. It was demonstrated in preceding studies that the selective formation of final products relied on the appropriate choice of Lewis acids. Interestingly, in this interrupted Nazarov reaction, the diastereoselectivity of the [3+2] cyclization is Lewis acid-dependent. The boron enolate added into the silicon-stabilized carbocation *anti* to the fused ring, while the bulkier tin enolate added *syn* to the fused ring (Scheme 1.9).

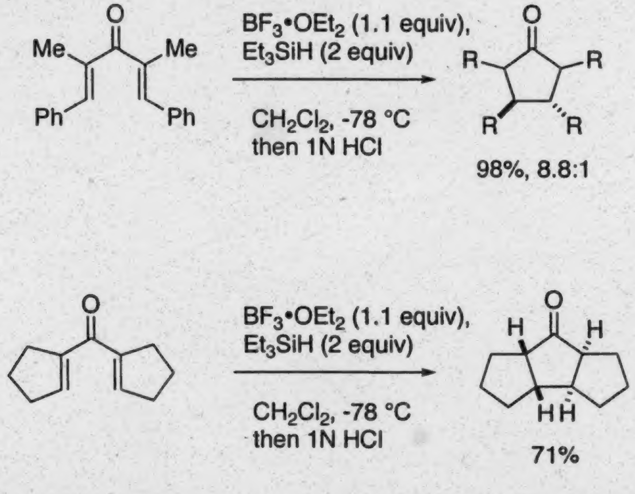
1.5.2 The Reductive Nazarov Cyclization

The existence of numerous cyclopentanoid natural products has led to the ongoing search and discovery of new methods for cyclopentannulation processes. Giese and West have shown that the oxyallyl intermediate formed during Nazarov cyclization could be reduced by intermolecular hydride delivery with a Lewis acid–stable hydride source Et_3SiH.[18] In this process, acyclic dienones are converted into cyclopentanones or their enol silanes (Scheme 1.10). As a result, this process has an advantage over the classical Nazarov cyclization by preserving the stereocenters formed after electrocyclization, and potentially controlling the two newly formed sterocenters by selective hydride delivery and selective enolate protonation.


MXn
R3SiH
R3SiX
OMXn
OMXn-1
OSiR3
Or

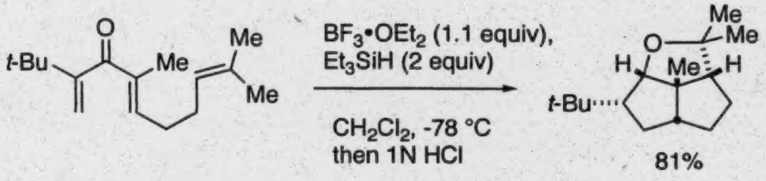
Scheme 1.10 The Reductive Nazarov Cyclization

Several dienones have been cyclized under various Lewis acidic conditions in the presence of triethylsilane. Treating the Nazarov substrates with $BF_3 \cdot OEt_2$ in the presence of triethylsilane led to the formation of cyclopentanones in high yields and diastereoselectivity (Scheme 1.11).


BF3•OEt2 (1.1 equiv), Et3SiH (2 equiv)
CH2Cl2, -78 °C then 1N HCl
98%, 8.8:1
BF3•OEt2 (1.1 equiv), Et3SiH (2 equiv)
CH2Cl2, -78 °C then 1N HCl
71%

Scheme 1.11 Cylcopentanone Formation *via* Reductive Nazarov Cyclization

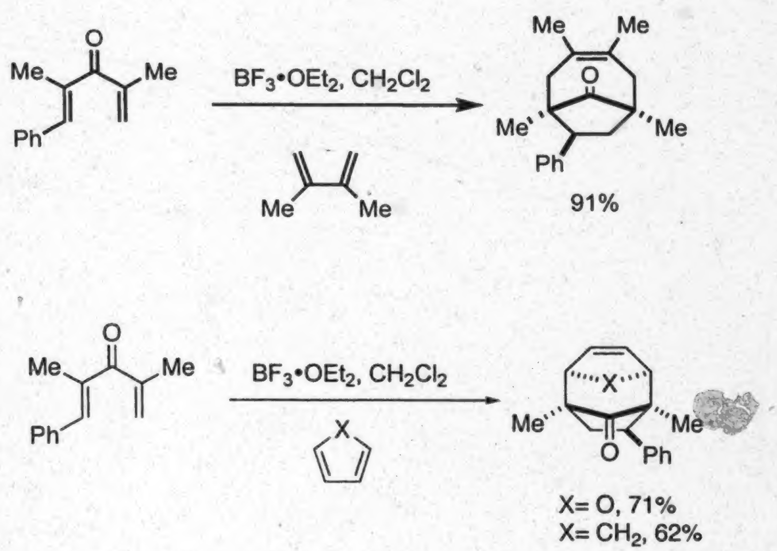
When a dienone, bearing a pendant alkene, was treated with $BF_3{\bullet}OEt_2$ in the presence of triethylsilane, no oxyallyl carbocation or tertiary carbocation trapping with hydride was seen. The only product was a tricyclic compound resulting from 5-*exo* cyclization followed by ionic hydrogenation of the resulting enol ether (Scheme 1.12).



Scheme 1.12 5-*exo* Cyclization

1.5.3 Intermolecular [4+3] trapping of the Nazarov Intermediate with 1,3-Dienes

Countless methods have been developed for the construction of the cyclooctanoid ring system. In particular, the [4+4] approach has been praised for its simplicity and selectivity. West and coworkers have shown that a simple 1,4-dien-3-one and 1,3-diene in the presence of $BF_3{\bullet}OEt_2$ could undergo a "domino" Nazarov electrocyclization /intermolecular [4+3]-cycloaddition pattern to furnish keto-bridged cyclooctenes in relatively good yield and diastereoselectivity.[19] Cyclopentadiene and furan underwent the cycloaddition reaction to generate the tricyclic compounds (Scheme 1.13).

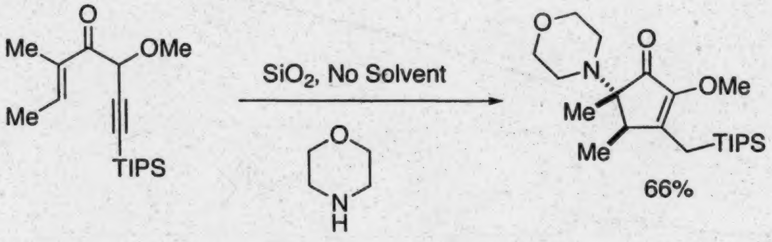

O
Me
Me
Ph
BF3•OEt2, CH2Cl2
Me
Me
Me
Me
O
Me
Me
Ph
91%
O
Me
Me
Ph
BF3•OEt2, CH2Cl2
X
X
Me
Me
O
Ph
X= O, 71%
X= CH2, 62%

Scheme 1.13 Intermolecular [4+3] Cycloaddition

In the case of acyclic dienes, excellent yields were obtained. Using an unsymmetrical diene like isoprene led to the formation of a 5:1 mixture of regioisomers. With a symmetrical diene like 2,3-dimethylbutadiene, a single diastereomer was formed The diastereoselectivity could be rationalized based on the approach of the diene farthest from the bulky β-substituent (Scheme 1.13).

1.5.4 Amine Trapping of the Nazarov Intermediate on Silica Gel

All previous work in the area of the interrupted Nazarov cyclization was based on the interception of the generated oxyallyl intermediate with electron rich carbo-nucleophiles, forming multiple carbon-carbon bonds in a single-step process. However, Dhoro and Tius have recently reported the amine trapping of the Nazarov oxyallyl intermediate, which forms aminocyclopentenones in the absence of solvent. This was the first example of nitrogen trapping of the Nazarov intermediate (Scheme. 1.14).[20] The stereochemistry of the product was explained by approach of the amine nucleophile from the less hindered face of the oxyallyl carbocation.



Scheme 1.14 Amine Trapping of the Nazarov Intermediate on Silica Gel

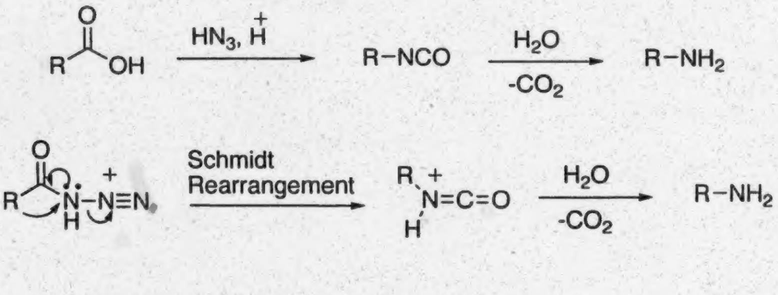
1.6 Organic Azide

Since the discovery of organic azide, phenyl azide, by Peter Grieβ[21] in 1864 these energy-rich and flexible intermediates have received considerable attention. There were many reactions involving these interesting species. One of these reactions involves azide rearrangements known as the Schmidt reaction.[21]

1.7 The Schmidt Reaction

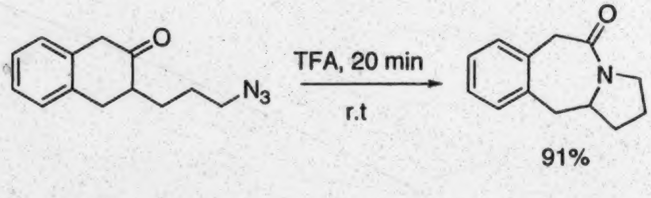
Reactions that include the addition of hydrazoic acid to carbonyl, or other compounds leading to insertion of a nitrogen atom into a chain or ring, are called Schmidt reactions. The most common form of the Schmidt reaction involves carboxylic acids.[21]

The mechanism of this reaction involves the rearrangement of the protonated azide (Scheme 1.15).



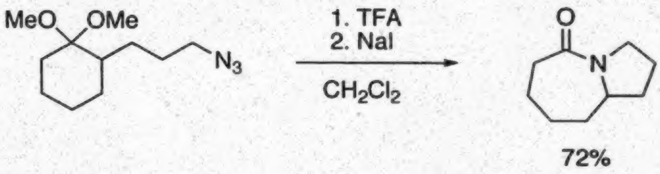
Scheme 1.15 The Schmidt Reaction

Aubé and co-workers have shown numerous examples of the Schmidt reaction of azido carbonyl and azido ketal compounds forming N-substituted lactams.[22] The first example of an intramolecular Schmidt reaction of alkyl azides was reported by Aubé and Milligan.[23] The synthesis of fused, bicyclic, and tricyclic lactams bearing a nitrogen atom at one of the ring fusion positions was carried out in this process. These reactions proceeded by treatment of cyclohexanones bearing an alkyl azide chain with Lewis acids or protic acids (Scheme 1.16).



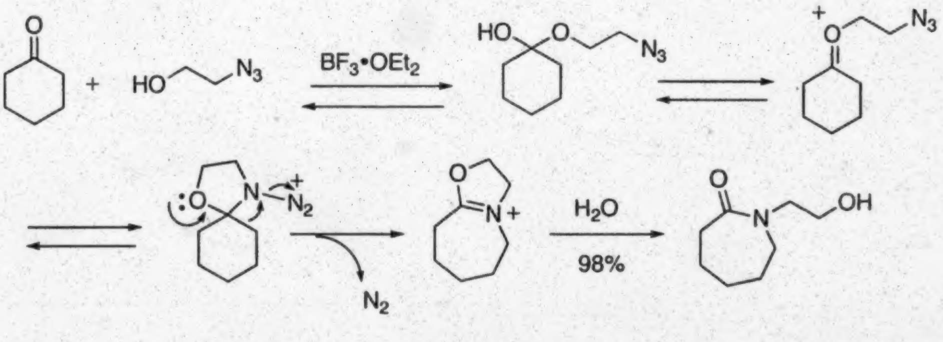
Scheme 1.16 Intramolecular Schmidt Reaction of Alkyl Azides

Not only were ketones viable substrates, but protected ketones could also undergo an intramolecular Schmidt reaction to afford bicyclic lactams (Scheme 1.17).[24]



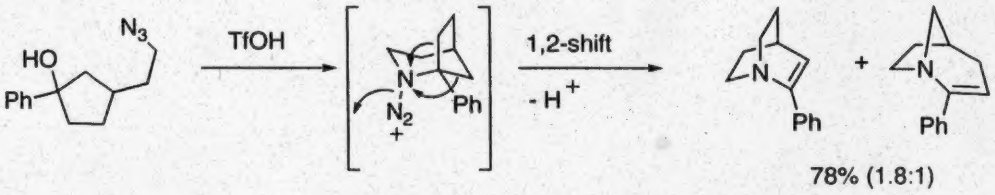
Scheme 1.17 Intramolecular Schmidt Reaction of Protected Ketones

Another example of intramolecular Schmidt reaction in which the ring expansion process facilitated by in Situ hemiketal formation has also been demonstrated by Aubé and co-workers, utilizing an azido alcohol.[25] In the presence of a Lewis acid, an oxocarbenium ion would be generated after the dehydration of the hemiketal. An intramolecular attack of the azide on the carbocation, followed by the migration of one of the alkyl groups and simultaneous loss of N_2, furnished an iminium ether species, which gave the desired lactam after hydrolysis (Scheme 1.18). This reaction led to the development of the "asymmetric Schmidt" rearrangement, which has been used in the synthesis of chiral lactams.[26]



Scheme 1.18 Intramolecular Schmidt Reaction Utilizing an Azido Alcohol

Pearson and co-workers have completed an intensive investigation on the reaction of organic azides distant from the carbocation, generated in a molecule (Scheme 1.19). [27]

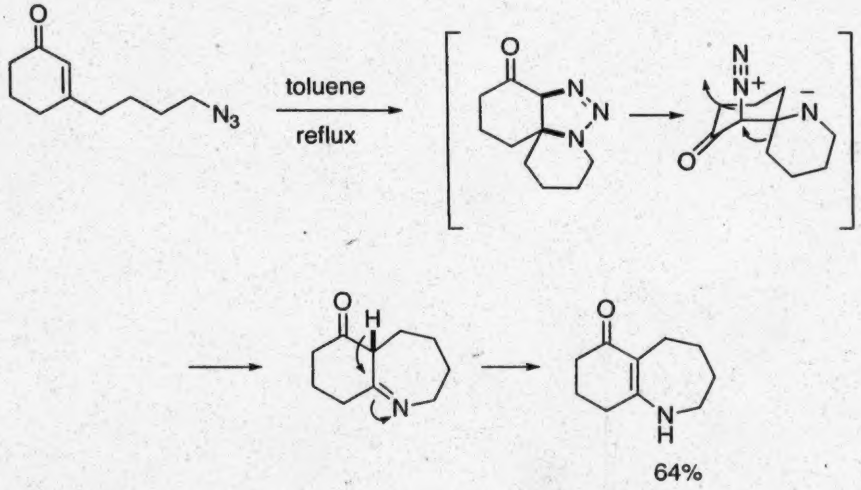


Scheme 1.19 Reaction of Organic Azides with Carbocation

In this process, protonation of the benzylic alcohol led to the generation of a tertiary carbocation, which forms the bicyclic intermediate after being attacked by the pendant azide. Migration of either of the substituents results in the loss of N_2 and generates a new carbocation. After deprotonation, two regiosiomers are formed, resulting from rearrangement of the aminodiazonium ion.

1.8 Intramolecular 1,3-Dipolar Cycloaddition of Alkyl Azide Enones

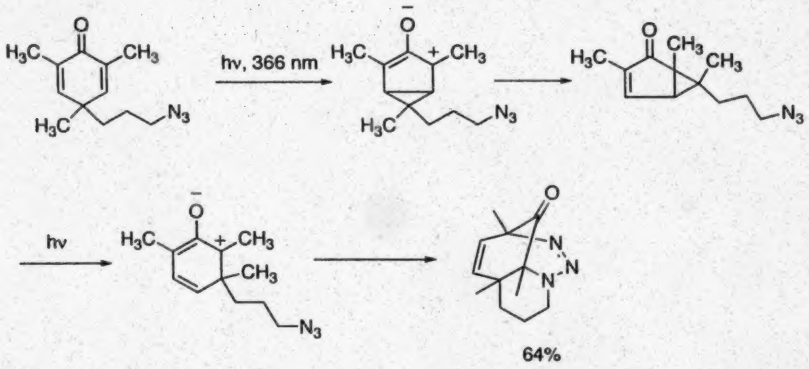
Sha and co-workers reported an intramolecular [1,3]-dipolar cycloaddition of alkyl azide enones,[28] where a cyclic enone bearing a pendant azide group has been heated in toluene, resulting in the formation of a bicyclic vinylogous amide. Initially, intramolecular cycloaddition of the azide enone would result in triazoline production. This unstable triazoline intermediate would then decompose to furnish the zwitterionic intermediate. The enaminone would be formed after a 1,2-alkyl shift, and elimination (Scheme 1.20).



Scheme 1.20 Intramolecular 1,3-Dipolar Cycloaddition of Alkyl Azide Enones

1.9 Intramolecular Azide Cycloaddition of Photochemically Generated Oxyallyl Cation

The first example of a [3+3] cycloaddition of the oxyallyl carbocation with azides was reported by Schultz and co-workers.[29] In this process, the oxyallyl carbocation was generated through photorearrangements of cyclohexadienone. The zwitterionic species was formed, and after a [1,4] sigmatropic shift, the cyclopropane bond cleaved and generated the oxyallyl carbocation. The final [3+3] cycloaddition with an azide then afforded the triazine product (Scheme 1.21).



Scheme 1.21 Intramolecular Azide Cycloaddition of Photochemically Generated Oxyallyl Cation

1.10 Summary and Outlook

In summary, many examples of the interrupted Nazarov reaction were discussed in this chapter. The interrupted Nazarov reaction has been established as one of the versatile and compatible reactions involving numerous types of nucleophilic additions to the Nazarov oxyallyl intermediate in a regio-and stereoselective manner. Multiple carbon-carbon bonds can be set in a single step along with a number of stereocenters.

All previous work in the area of the interrupted Nazarov cyclization was based on the interception of the generated oxyallyl intermediate with electron rich carbon nucleophiles. We decided to investigate the reaction of organoazides with the oxyallyl carbocation generated during Nazarov cyclization, which would be the seconed example of nitrogen trapping of the Nazarov intermediate.

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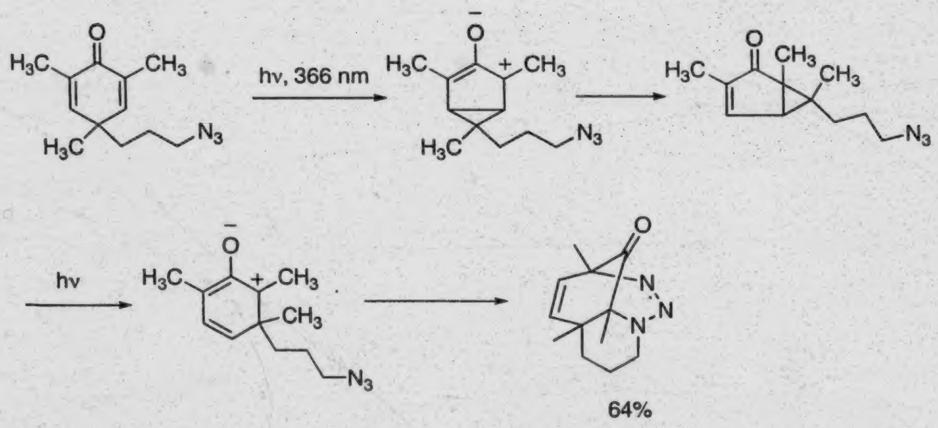
2 CHAPTER 2

2.1 The Inter- and Intramolecular Azide Trapping of The Nazarov Oxyallyl Intermediate

2.2 Background

Numerous polycyclic skeletal systems were discussed in the previous chapter were generated using the interrupted Nazarov process. In the course of Nazarov cyclization, which was fully outlined in the previous chapter, a reactive oxyallyl carbocation was produced after initial conrotatory electrocyclization. It has been shown that organoazides can undergo [3+3] cycloaddition chemistry with π systems related to the oxyallyl carbocation. We envisioned using this aspect of azide chemistry in the interrupted Nazarov reaction to build up novel heterocycles.

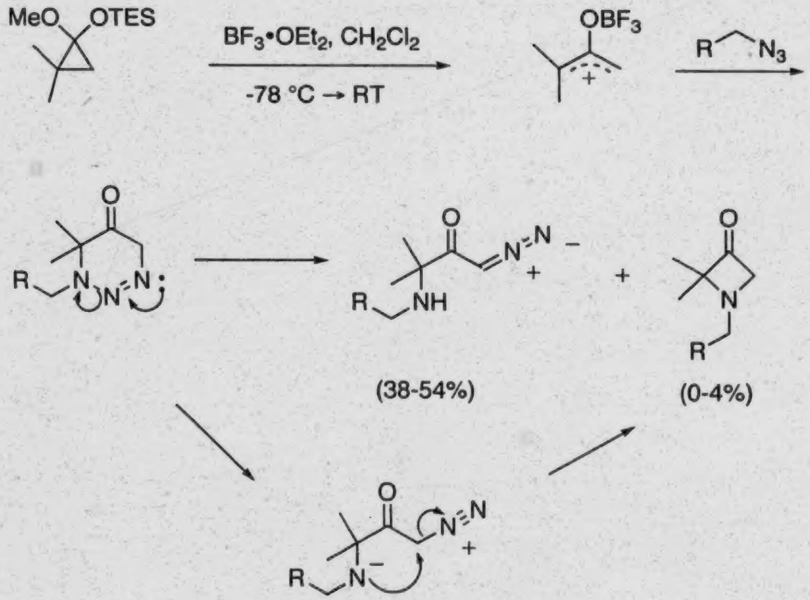
As mentioned in the previous chapter, the first example of the cycloaddition of an organoazide with the oxyallyl intermediate was reported by Schultz and co-workers.[1] During that process, the reactive oxyallyl intermediate generated through photorearrangement of cyclohexadienone subsequently underwent a [3+3] cycloaddition with a pendant azide to generate the triazine product (Scheme 2.1).



Scheme 2.1 Intramolecular Azide Cycloaddition of Photochemically Generated Oxyallyl Cation

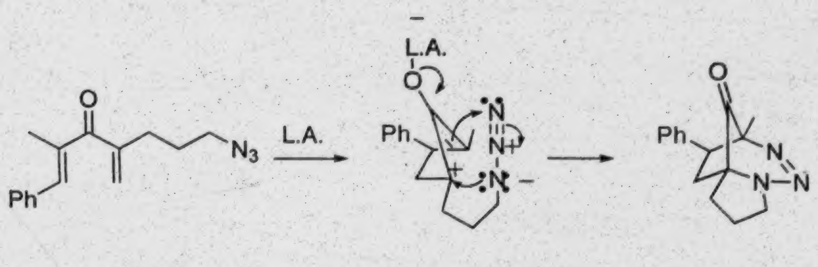
Desai and Aube[2] have shown that treating substituted cyclopropanone with $BF_3•OEt_2$ furnishes 2-oxyallyl carbocation after cleavage of the 2,3-bond. This reactive intermediate then underwent apparent [3+3] cycloaddition with an alkyl azide to form a 1,2,3-triazine-5-one intermediate. Subsequent ring opening followed by proton transfer formed α-amino-α′-diazomethyl ketones and small amounts of 3-azetidinones.

The presence of 3-azetidinones is explained by either an acid-promoted decomposition of the diazoketone or from the direct cyclization pathway. Diazoketones are highly useful synthetic intermediates that are normally made by diazomethane addition to an acyl chloride or by diazo transfer.[3] The illustrated process is an alternative way of generating diazoketones (Scheme 2.2).

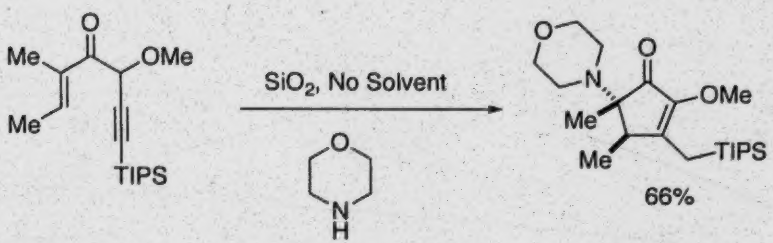


Scheme 2.2 Ring Opening of Substituted Cyclopropanones with Alkyl Azides

In order to examine the possibility of triazine formation, we decided to investigate the reaction of organoazides with the oxyallyl carbocation generated during Nazarov cyclization which would be the first example of nitrogen trapping of the Nazarov intermediate (Scheme 2.3). While developing this chemistry, Tius and Dhoro published the result of amine trapping of the oxyallyl carbocation generated under unusual Nazarov cyclization conditions (Scheme 2.4).[4]



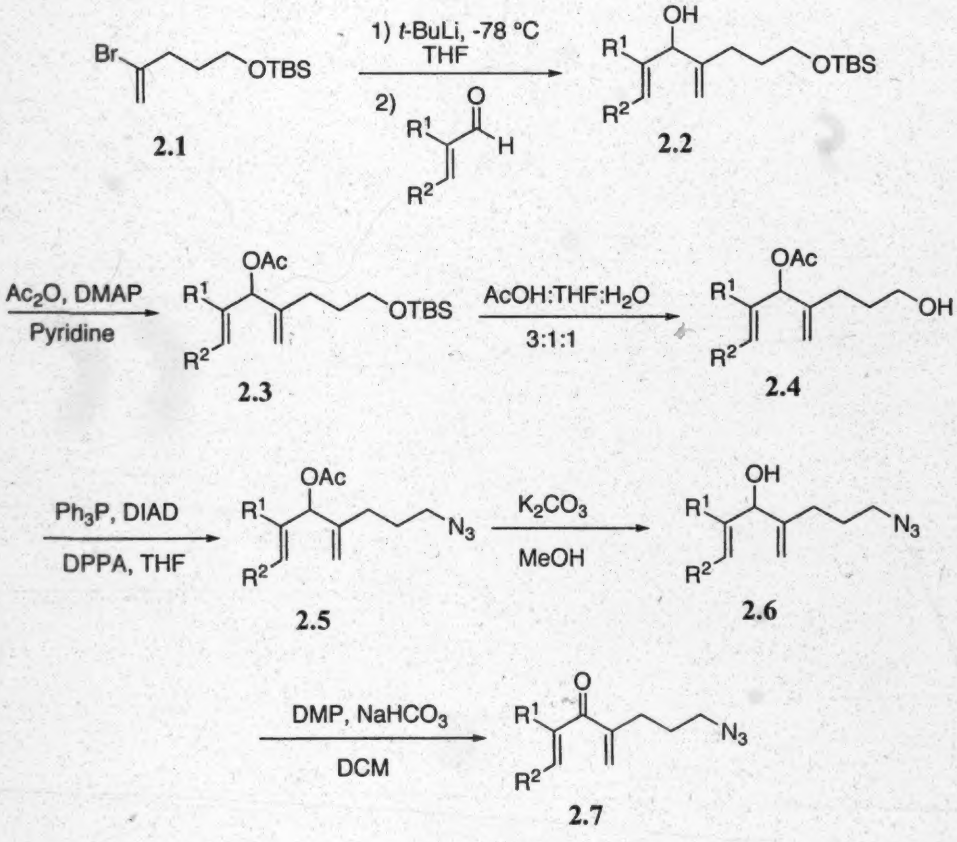
Scheme 2.3 [3+3] Cycloaddition of the Nazarov Oxyallyl Intermediate with Azides



Scheme 2.4 Amine Trapping of the Nazarov Intermediate on Silica Gel

2.3 Preparation of Dienones

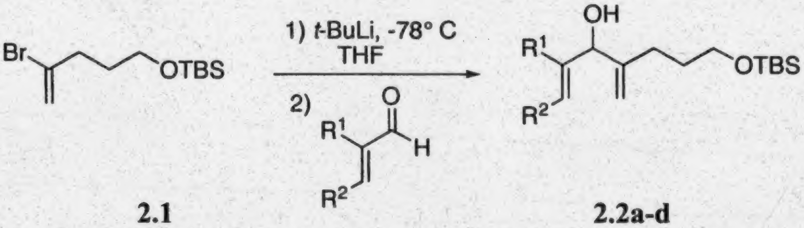
In order to investigate intramolecular azide trapping in the interrupted Nazarov reaction, dienone substrates with tethered azides were required. First the azide functionality was installed onto the vinylbromide alkyl chain before the addition of the organolithium intermediate in to the corresponding aldehydes. This sequence failed to give the desired dienol. Protection of the primary alcohol with the TBS group before formation of the organolithium intermediate and protection of the secondary bis-allylic alcohol before installation of the azide group were necessary for making the corresponding dienones. The general approach used in the synthesis of the different dienones was straightforward (Scheme 2.5). The known vinyl bromide **2.1**[5] was subjected to *t*-BuLi, generating the corresponding anion. Subsequent addition of aldehyde provided the dienol **2.2**. Protection of the dienol with acetate furnished the bis-protected dienol **2.3**. Selective deprotection of the primary alcohol under acidic conditions provided alcohol **2.4**. Transformation of the primary alcohol to the corresponding azide **2.5** was accomplished *via* the Mitsunobu reaction. Basic deprotection of the secondary alcohol, followed by oxidation with Dess-Martin periodinane, provided the desired dienone **2.7**.


Br
OTBS
2.1
1) t-BuLi, -78 °C
THF
2)
O
R1
H
R2
OH
R1
R2
OTBS
2.2
Ac2O, DMAP
Pyridine
OAc
R1
R2
OTBS
2.3
AcOH:THF:H2O
3:1:1
OAc
R1
R2
OH
2.4
Ph3P, DIAD
DPPA, THF
OAc
R1
R2
N3
2.5
K2CO3
MeOH
OH
R1
R2
N3
2.6
DMP, NaHCO3
DCM
O
R1
R2
N3
2.7

Scheme 2.5 Preparation of Dienones

2.3.1 Preparation of Dienols 2.2a-d

The desired dienols **2.2a-d** were prepared via anionic addition of the corresponding vinyl bromide **2.1** to α,β-unsaturated aldehydes bearing different substituents (Table 2.1).



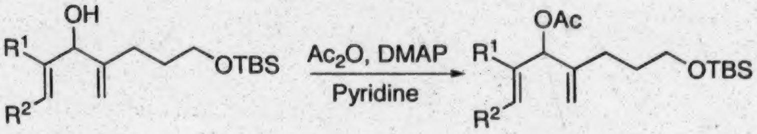
2.1 **2.2a-d**

entry	R^1	R^2	product	yield (%)
1	Me	Ph	**2.2a**	63
2	Me	H	**2.2b**	63
3	-$(CH_2)_4$-		**2.2c**	71
4	-$(CH_2)_3$-		**2.2d**	65

Table 2.1 Preparation of Dienols **2.2a-d**

2.3.2 Preparation of Bis-protected Dienols 2.3a-d

The bis-allylic alcohols were protected as the acetates to provide compounds **2.3a-d** (Table 2.2).



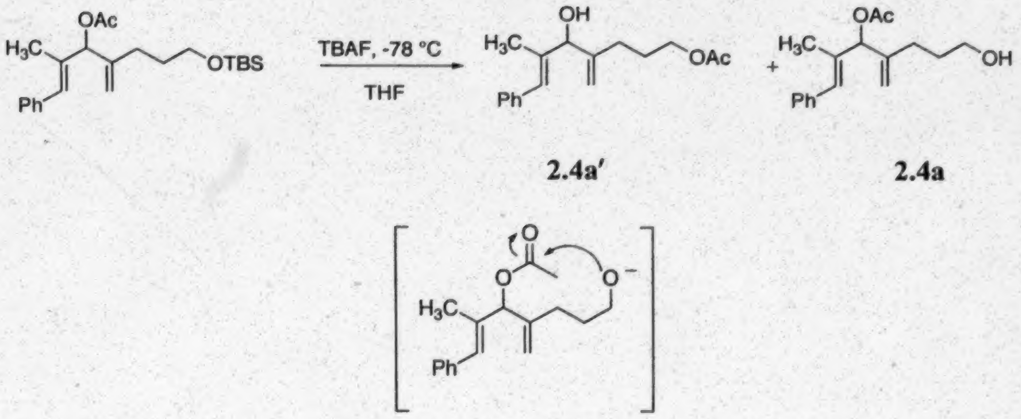
2.3a-d

entry	R^1	R^2	product	yield (%)
1	Me	Ph	**2.3a**	78
2	Me	H	**2.3b**	96
3	-(CH$_2$)$_4$-		**2.3c**	78
4	-(CH$_2$)$_3$-		**2.3d**	87

Table 2.2 Preparation of Bis-protected Dienols **2.3a-d**

2.3.3 Preparation of alcohols **2.4a-d**

The TBS-protected alcohol **2.3a** was subjected to TBAF in THF at -78 °C for the selective removal of the TBS group in the presence of the acetate functionality. Unfortunately the acyl transfer product was obtained along with the deprotected primary alcohol. The formation of this undesired product has been attributed to an intramolecular transesterification process *via* intermediate **2.4a**" under the basic conditions of the desilylation (Scheme 2.6).[6]



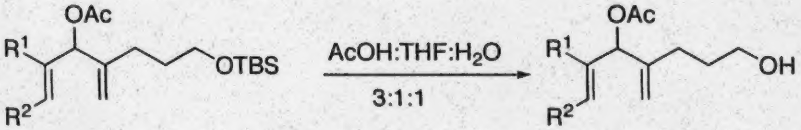
2.4a′

2.4a

2.4a"

Scheme 2.6 Preparation of Alcohols **2.4a-d**

As a result of this undesirable side-reaction, an alternative method for deprotection of the primary TBS group was used (Table 2.3). Corey and Venkateswarlu[7] reported that a TBS ether could be deprotected under mild acidic conditions involving AcOH, H_2O, THF (3:1:1). Application of this method to compounds **2.3a-d** gave the desired mono-protected alcohols **2.4a-d**. The desired compound **2.4a** was distinguished from compound **2.4a′** based on the chemical shift of a methylene proton adjacent to an ester (4.1 ppm) versus the methylene protons of the primary alcohol (3.7 ppm).



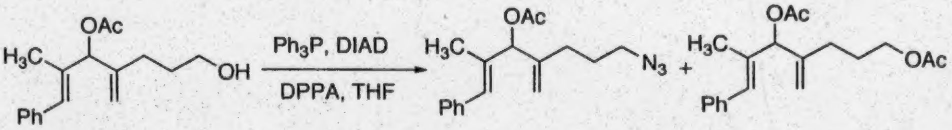
2.4a-d

entry	R^1	R^2	product	yield (%)
1	Me	Ph	**2.4a**	88
2	Me	H	**2.4b**	73
3	-$(CH_2)_4$-		**2.4c**	78
4	-$(CH_2)_3$-		**2.4d**	82

Table 2.3 Mild Acid Deprotection of the TBS Ether

2.3.4 Preparation of Azido Compounds **2.5a-d**

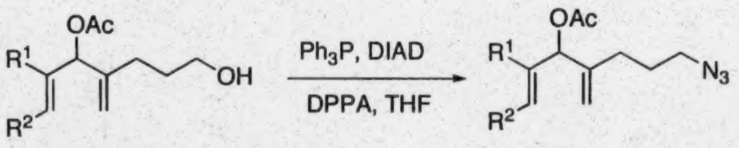
The transformation of primary alcohols **2.4a-d** to the desired azides **2.5a-d** was accomplished using the Mitsunobu protocol.[8a] Unfortunately, a side-reaction product **2.5a′** was obtained along with the desired azide product. The formation of acetate compound **2.5a′** from the primary alcohol was most likely related to the presence of acetic acid residuse from the previous reaction, which could act as an alternate nucleophile in the Mitsunobu reaction. (Scheme 2.7)



2.5a **2.5a′**

Scheme 2.7 Acetate Substitution in the Mitsunobu Reaction

To avoid formation of **2.5a′**, it was necessary to eliminate all traces of acetic acid. Thus, the primary alcohol substrate was washed repeatedly with a basic solution of sodium bicarbonate. Consequently, the desired azide product was obtained without the formation of any byproducts (Table 2.4).



2.5a-d

entry	R^1	R^2	product	yield (%)
1	Me	Ph	**2.5a**	85
2	Me	H	**2.5b**	70
3	-$(CH_2)_4$-		**2.5c**	73
4	-$(CH_2)_3$-		**2.5d**	90

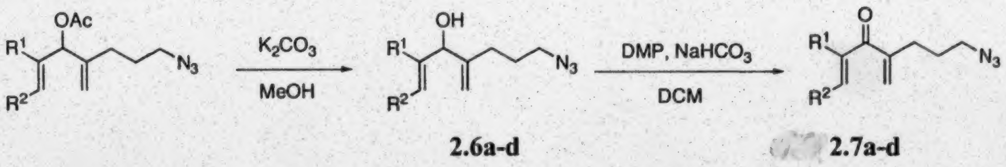
Table 2.4 Preparation of Azido Compounds **2.5a-d**

2.3.5 Preparation of Azido Alcohols **2.6a-d**

Deprotection of the bis-allylic alcohol was performed under basic conditions using K_2CO_3 in methanol. The reaction was stirred overnight to gain the desired alcohol in high yield. The crude product was carried on to the next step without further purification

2.3.6 Preparation of Dienones **2.7a-d**

The desired dienones were prepared from oxidiation of the crude dienols **2.6a-d** with Dess-Martin periodinane reagent under buffered conditions (6 equiv. $NaHCO_3$).[9] Under these conditions, the desired dienones **2.7a-d** bearing the pendant azide were formed in high yields (Table 2.5).

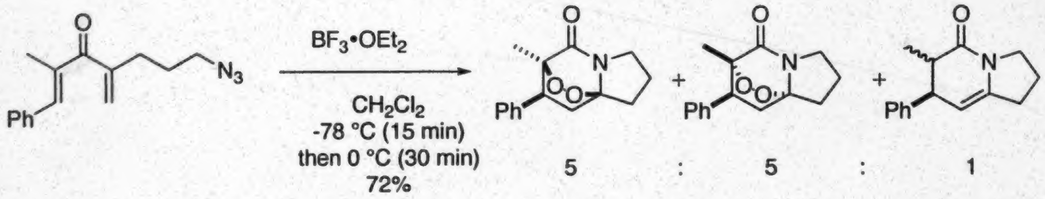


entry	R^1	R^2	product	yield (%)
1	Me	Ph	**2.7a**	71
2	Me	H	**2.7b**	58
3	-$(CH_2)_4$-		**2.7c**	70
4	-$(CH_2)_3$-		**2.7d**	68

Table 2.5 Preparation of Dienones **2.7a-d**

2.4 Cyclization of Substituted Dienones and Structure Determination of Novel Products

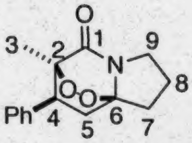
It was hoped that submitting dienones with a pendant azide group to the Lewis acid conditions would lead to the formation of triazine products. Treatment of substrate **2.7a** with BF_3•OEt_2 at -78 °C for 15 minutes, followed by 30 minutes at 0 °C, produced a 5:5:1 mixture of three isomers containing a bicyclic amide moiety. The polarity of these compounds was much higher than the starting substrate and they could be detected by anisaldehyde staining of silica TLC plates. After separation by column chromatography, the three products were fully characterized by 1D and 2D NMR studies and an X-ray analysis of **2.8a** rigorously established the relative stereochemistry (Scheme. 2.8).



2.7a **2.8a** **2.8b** **2.9**

Scheme 2.8 Cyclization of Substrate **2.7a**

2.4.1 Structure Determination of Tricyclic Compound **2.8a**



2.8a

Carbon Number	δ_C (ppm)	δ_H (ppm)
1	167.1 (C)	
2	82.8 (C)	
3	14.9 (CH_3)	1.2 (s, 3H)
4	47.0 (CH)	3.52 (dd, 1H, *J* = 10.1, 4.9 Hz)
5	38.8 (CH_2)	2.84 (dd, 1H, *J* = 13.4, 10.1 Hz), 1.89 (dd, 1H, *J* = 13.0, 5.0 Hz)
6	95.0 (C)	
7	23.1 (CH_2)	2.1-2.3 (m, 2H)
8	34.6 (CH_2)	2.1-2.3 (m, 2H)
9	45.0(CH_2)	3.7 (ddd, 1H, *J* = 7.3, 5.8, 3.6 Hz), 3.96-4.02 (m, 1H)

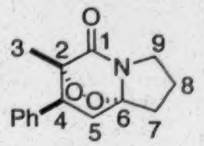
Table 2.6 Chemical Shifts of Tricyclic Compound **2.8a**

H Number	COSY correlation
1	
2	
3	
4	H5, H5'
5	H5, H5', H4
6	
7	H7, H7', H8, H8'
8	H8, H8',H7, H7', H9, H9'
9	H9, H9', H8, H8'

Table 2.7 Correlations in COSY Spectra of Tricyclic Compound **2.8a**

The electrospray ionization mass spectrum identified the molecular formula as $C_{15}H_{17}NO_3$, which contained eight units of unsaturation. The structure of compound **2.8a** was determined by NMR spectral data (Table 2.6 and 2.7). The following assignments were based on ^{13}C NMR and ^1H NMR experiments. The carbon (C1) at 167.1 ppm was assigned as an amide carbonyl carbon. Carbons at 82.8 ppm and 95.0 ppm (C2 and C6, respectively) were the bridgehead carbons connected to the peroxy oxygens. Higher chemical shifts of these two carbons indicated that they were attached to electronegative atoms. The methyl carbon (C3) at 14.9 ppm was connected to a bridgehead carbon. The fact that both carbon and protons at this position have higher chemical shifts and that the methyl protons appeared as a singlet suggested this assignment. The carbon at 47.0 ppm was the methine C4. The methine proton H4 had two correlations with methylene protons at C5 by a large coupling constant (10.1 Hz) and a smaller one (4.9 Hz). Diastereotopic methylene protons H5 and H5$'$, which were correlated in the COSY spectrum, were connected to the carbon at 38.8 ppm (C5). The methylene carbons C7, C8, and C9 at 45.0 ppm, 34.6 ppm, and 23.1 ppm were assigned to the three methylene units in the isolated five membered ring system based on COSY and HMQC spectra. In table 2.6, protons were shown to be directly attached to the corresponding carbons by a HMQC experiment. With NMR and X-ray data in hand, the structure of compound **2.8a** was elucidated (Scheme 2.8).

2.4.2 Structure Determination of Tricyclic Compound **2.8b**



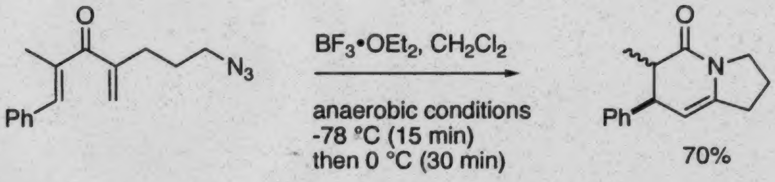
2.8b

Carbon Number	δ_C (ppm)	δ_H (ppm)
1	168.4 (C)	
2	82.1 (C)	
3	14.4 (CH_3)	1.0 (s, 3H)
4	44.4 (CH)	3.18 (dd, 1H, *J* = 11.5, 5.5 Hz)
5	38.4 (CH_2)	2.46 (dd, 1H, *J* = 13.5, 5.4 Hz), 2.37 (dd, 1H, *J* = 13.5, 11.5 Hz)
6	95.2 (C)	
7	23.1 (CH_2)	2.10-2.30 (m, 1H), 1.99-2.06 (m, 1H)
8	34.6 (CH_2)	2.10-2.30 (m, 2H)
9	44.8 (CH_2)	3.9 (ddd, 1H, *J* = 11.5, 7.3, 5.0 Hz), 3.56-3.62 (m, 1H)

Table 2.8 Chemical Shifts of Tricyclic Compound **2.8b**

The electrospray ionization mass spectrum for **2.8b** identified the molecular formula as $C_{15}H_{17}NO_3$, containing eight units of unsaturation. This data suggested that compound **2.8b** could be a diastereoisomer of compound **2.8a**.The structure of compound **2.8b** was determined by NMR spectral data (Table 2.8). The following assignments were based on ^{13}C NMR and ^{1}H NMR experiments. The carbon at 168.4 ppm was assigned as an amide carbonyl carbon (C1). Quaternary carbons at 95.2 ppm and 82.1 ppm (C6 and C2, respectively) were assigned to bridgehead carbons connected to the peroxy oxygens, as implied by their high chemical shifts. Also, the 2D HMBC spectrum showed a correlation between C2 and the methyl protons H3 at 1.0 ppm. These protons appeared as a singlet in the ^{1}H NMR spectrum. The carbon at 44.4 ppm was determined to be a methine carbon whose proton showed correlations with methylene protons H5 and H5′ (2.46 ppm) in the COSY spectrum. As observed in **2.8a**, there are three isolated methylene carbons in the five membered ring system. The carbon at 23.1 ppm was assigned to C7 whose methylene protons H7 and H7′ show correlations with C6 in the HMBC spectrum. The carbons at 34.6 ppm and 44.8 ppm were assigned to be C8 and C9 respectively based on correlations in COSY and HMQC spectra. The assigned stereochemistry was based on spectral analogy to **2.8a**

The presence of a peroxy bridge in two of the products, and its absence in other product **2.9**, prompted us to perform this reaction under rigorously anaerobic conditions. This anaerobic condition was established *via* purging both solutions of dienones and Lewis acid before their admixture and careful Schlenck technique has been used to exclude the air oxygen from the reaction media. Subjecting dienone **2.7a** to BF_3•OEt_2 under this anaerobic environment led to the formation of bicyclic amide **2.9** as the sole product. The relative stereochemistry of the major product assigned as *trans* based on the large *J* = 7.2 Hz (Scheme 2.9).

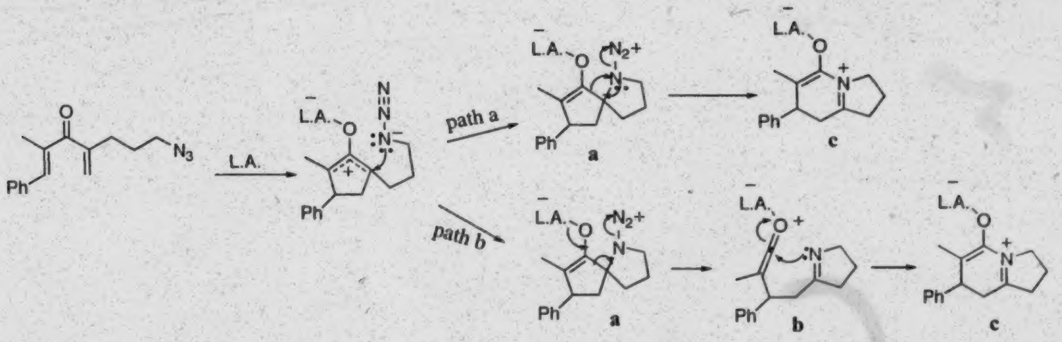


2.7a **2.9**

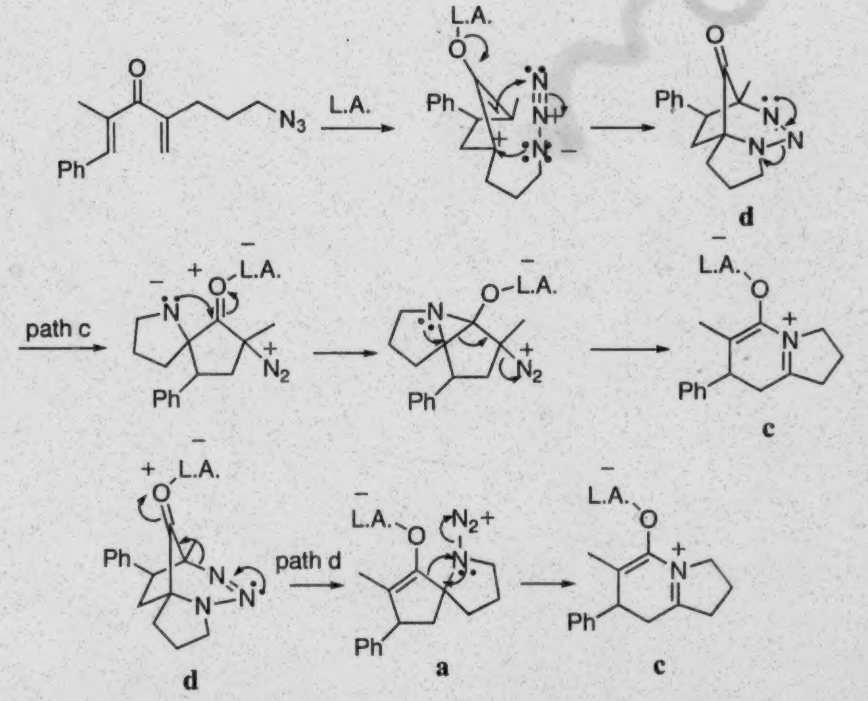
Scheme 2.9 Preparation of Compound **2.9**

2.5 Proposed Mechanism

Treatment of substrate **2.7a** with $BF_3 \bullet OEt_2$ is presumed to result in the formation of cyclic oxyallyl carbocation *via* a 4π-electrocyclization Nazarov process. Three possible reaction pathways involving the oxyallyl intermediate and the pendant azide can be envisioned. The first pathway involves nucleophilic attack of the internal azide nitrogen on to the oxyallyl carbocation followed by a 1,2-shift from the quaternary carbon to the azide nitrogen atom with concomitant loss of N_2 (intermediate **a)** to directly form the 1,4-dipolar intermediate **c** (path a, Scheme 2.10). The seconed pathway could involve Lewis acid assisted bond migration with loss of N_2 to generate a ketene-imine intermediate **b**, which could lead to the 1,4-dipole **c** after reassembly (path b, Scheme 2.10). In the third pathway, the oxyallyl carbocation could undergo the expected [3+3]-cycloaddition reaction with azide to generate a triazine intermediate **d** (Scheme 2.11).[2] This intermediate would then undergo ring opening via two pathways (path c and path d) followed by rearrangement to generate the 1,4-dipole intermediate **c**. Regardless of the mechanism of its formation, the 1,4-dipole is expected to be highly reactive and short-lived, either reacting with ambient oxygen to give peroxides **2.8a,b**, or rearranging to **2.9.**[10]


L.A.
path a
path b
a
b
c
Ph

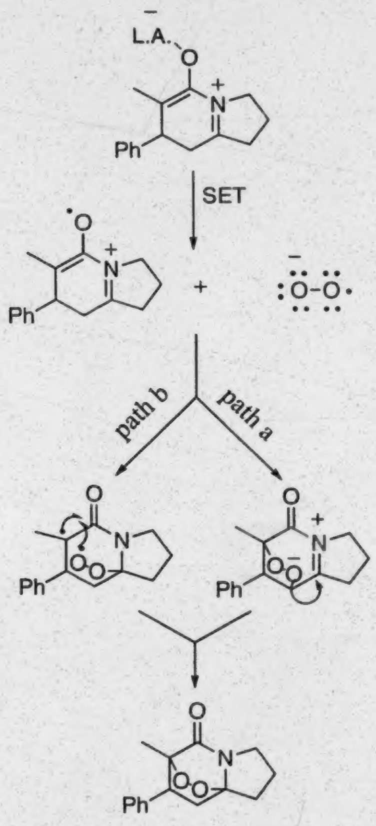
Scheme 2.10 Proposed Mechanism for 1,4-Dipole Formation *via* Nitrogen-Centered Nucleophile


L.A.
path c
path d
a
c
d
Ph

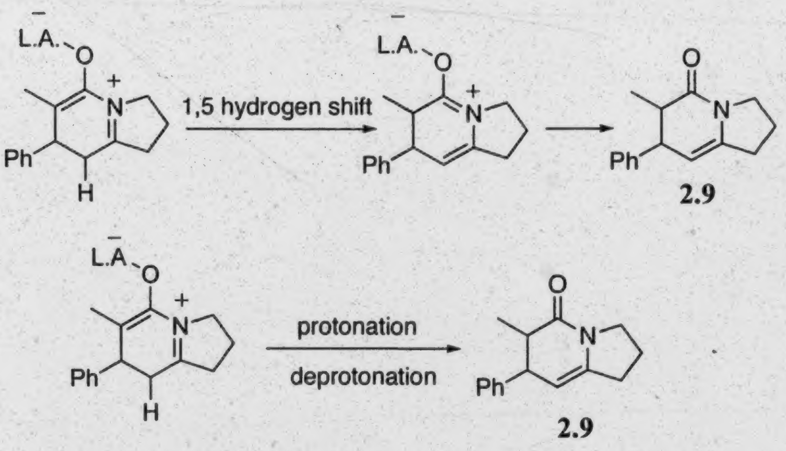
Scheme 2.11 Proposed Mechanism for 1,4-Dipole Formation via [3+3] Process

In contrast to 1,3-dipoles, much less is known about the cycloaddition behavior of 1,4-dipoles. The synthetic utility of these highly reactive intermediates has been limited until the units of 1,4-dipoles were integrated into cross-conjugated heteroaromatic betaines.[10] These electron-rich intermediates could undergo several types of either inter- or intramolecular cycloaddition reactions with either electron rich or electron poor dipolarophiles.

The most common route to endoperoxides such as **2.8a,b** mainly arises from the reaction of a simple 1,3-diene with photoinduced singlet oxygen.[11] Although generation of these structures is rare under non-photochemical conditions, there are a limited number of examples in the literature showing the reaction of a 1,3-diene with triplet oxygen.[12] Reaction of highly electron-rich 1,4-dipoles with triplet oxygen could be rationalized as follows: a single electron transfer (SET) from the enolate oxygen would form a radical cation/radical anion pair which would subsequently recombine. The reaction of superoxide radical anion and the 1,4-dipole radical cation could proceed by one of two pathways, either a radical coupling of superoxide and the 1,4-dipole intermediate followed by anionic addition (path a), or by anionic addition followed by radical coupling (path b) to generate the endoperoxide products (Scheme 2.12). Formation of two endoperoxide isomers in the case of substrate **2.7a** is based on two different approaches of oxygen on to the generated 1,4-dipole. This approach could be either *syn* or *anti* to the phenyl group, which has its stereochemistry established in the course of the electrocyclization step. Generation of the third product, **2.9**, is probably as a result of a [1,5]-hydrogen shift or proton transfer sequence (Scheme 2.13).


L.A.
SET
path b
path a
Ph

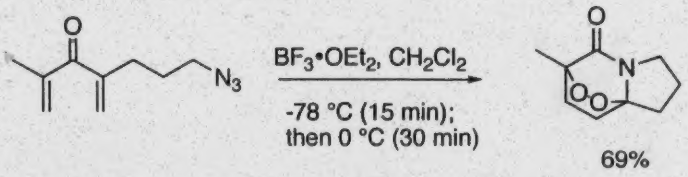
Scheme 2.12 Proposed Mechanism for Peroxy-Bridge Formation


L.A.
1,5 hydrogen shift
Ph
H
2.9
protonation
deprotonation
2.9

Scheme 2.13 Proposed Mechanism for the Formation of Compound **2.9**

It has been shown that the presence of β-substitution on the dienone is essential for domino Nazarov cyclization/[4+3] cycloaddition reaction,[13] probably due to the short lifetime of the substrates in the presence of strong Lewis acids. Also, Denmark[14] and Torssell[15] reported that β-substitution is crucial for the success of the initial electrocyclization process. They proposed that such substitution might reduce the reactivity of the dienone as a Michael acceptor, thereby minimizing unwanted side reactions. Considering these previous observations, we were curious to test the feasibility of the analogous azide reaction in the absence of any β-substitution.

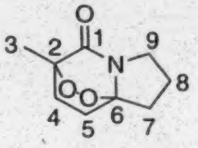
Treatment of dienone **2.7b** with $BF_3 \cdot OEt_2$ at -78 °C led to the formation of the tricyclic amide **2.10** containing a peroxy-bridge. The generation of this product showed that reaction of alkyl azides with the oxyallyl carbocation generated during the Nazarov cyclization was quite a rapid process (Scheme 2.14). Importantly, the absence of any β-substituents removed the possibility of forming diastereomeric products, and indeed only a single product was obtained. The non-oxygenated 1,5-shift product was not obtained in this case.



2.7b **2.10**

Scheme 2.14 Preparation of Compound **2.10**

2.5.1 Structure Determination of Tricyclic Compound 2.10



2.10

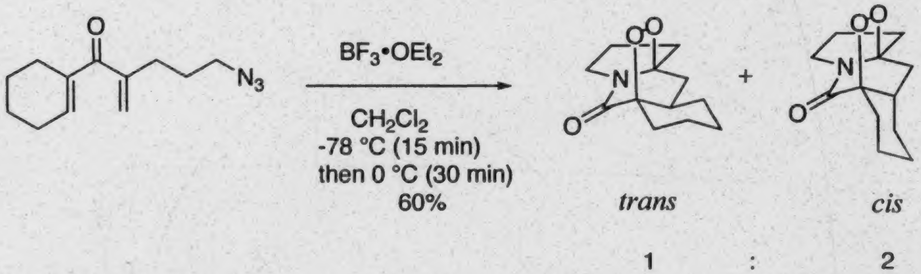
Carbon Number	δ_C (ppm)	δ_H (ppm)
1	168.5 (C)	
2	79.6 (C)	
3	16.5 (CH_3)	1.36 (d, 3H, $J = 0.8$ Hz)
4	29.4 (CH_2)	2.20-2.38 (m, 2H)
5	29.3 (CH_2)	1.90-2.00 (m, 1H), 1.74-1.84 (app dt, 1H, $J = 11.5, 2.4$ Hz)
6	95.5 (C)	
7	23.3 (CH_2)	1.90-2.00 (m, 1H),2.02-2.14 (m, 1H)
8	34.7 (CH_2)	2.02-2.14 (m, 2H)
9	44.9(CH_2)	3.80-3.90 (m, 1Hz) 3.5 (app dt, 1H, $J = 11.7, 6.5$ Hz)

Table 2.9 Chemical Shifts of Tricyclic Compound **2.10**

The electrospray ionization mass spectrum provided a molecular formula of $C_9H_{13}NO_3$. The IR spectrum showed a strong signal at 1690 cm^{-1} which was a typical signal for amide carbonyl stretching. The structure of compound **2.10** was determined by NMR spectral data. Two diastereotopic protons H9 and H9′ were separated from other methylene protons because of the inductive electron-withdrawing effect of the polar amide moiety. From the HMBC spectrum, correlations between C6 at 95.5 ppm with H5, H5′, H7 and H7′ methylene protons were observed which provided evidence for the proposed carbon skeleton. Protons (Table 2.9) were shown to be directly attached to the corresponding carbons by a HMQC experiment.

2.6 Cyclization of More Substituted Substrates

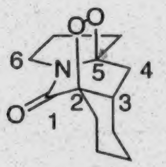
Substrates containing five-and six-membered ring systems were synthesized. Subjecting dienone **2.7c** to the previously outlined reaction conditions led to the formation of two diastereoisomers in a 2:1 ratio in favor of the *cis*- isomer. The relative stereochemistry was established based on the X-ray analysis of the *trans*-isomer after the reduction of the peroxy functional group, which will be discussed later in this chapter (Scheme 2.15).



2.11 **2.12**

Scheme 2.15 Cyclization of Dienone Containing a Six-Membered Ring System

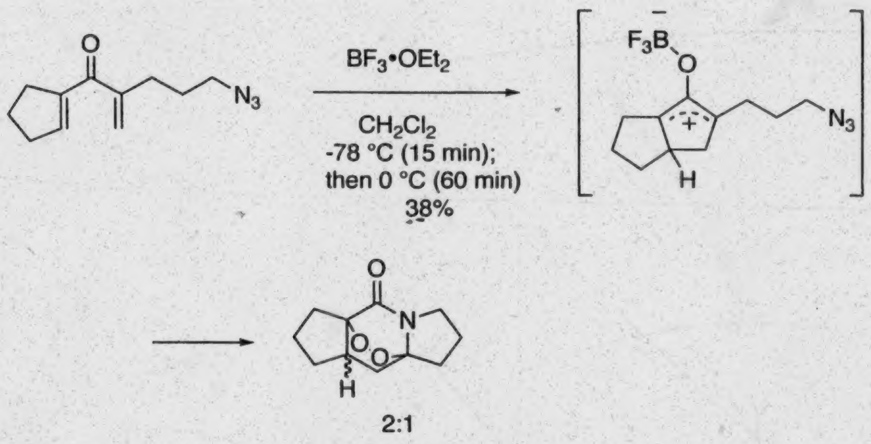
2.6.1 Structure Determination of Tetracyclic Compound 2.12



2.12

The electrospray ionization mass spectrum provided a molecular formula of $C_{12}H_{17}NO_3$. The IR spectrum showed a strong signal at 1690 cm^{-1} which is a typical absorbance for amide carbonyl stretching. The carbon (C1) at 167.5 ppm was assigned as an amide carbonyl carbon. Carbons at 81.8 ppm and 94.0 ppm (C2 and C5, respectively) were assigned as bridgehead carbons connected to the peroxy oxygens. The carbon at 37.6 ppm was identified as a methine, which correlates to a proton signal at 2.48 ppm in the HMQC spectrum. Diastereotopic protons at 3.40-3.50 ppm and 3.78-3.88 ppm correlate to the carbon (C6) at 44.7 ppm. The remaining methylene protons appear between 1-2 ppm with severe overlap and are difficult to assign to the corresponding carbons.

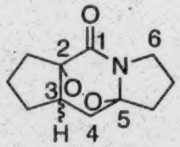
Cyclization of the dienone containing the five-membered ring system **2.7d** was accomplished by lengthening the reaction time and by using a higher temperature (0 °C). The two isomeric products (2:1 ratio) were formed in lower yield and one of them **2.13a** as an inseparable mixture of compounds. The other isomer **2.13b** were separated and purified. The lower yield is probably due to the strain associated with the presumed oxyallyl intermediate which led to a slower cyclization process and a less stable intermediate (Scheme 2.16).



2.13a : 2.13b

Scheme 2.16 Cyclization of Dienone Containing Five-Membered Ring System

2.6.2 Structure determination of Tetracyclic Compound **2.13b**

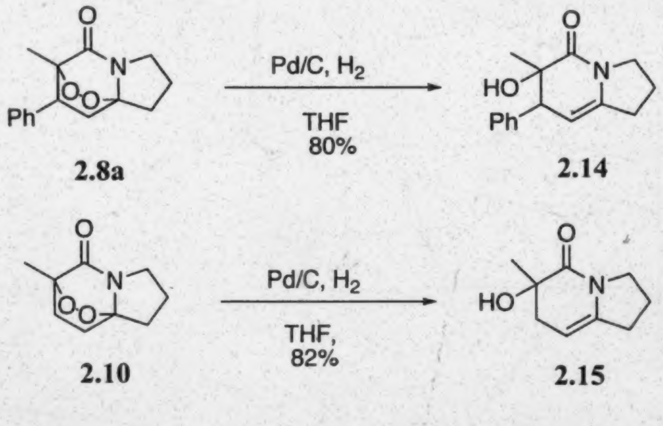


2.13b

The electrospray ionization mass spectrum provided the molecular formula of $C_{11}H_{15}NO_3$. The carbon (C1) at 168.7 ppm was assigned to the amide carbonyl carbon. Carbons at 90.1 ppm and 96.9 ppm (C2 and C5, respectively) were identified as bridgehead carbons connected to the peroxy oxygens. The carbon at 42.6 ppm was assessed as a methine (C3). Diastereotopic protons at 3.40-3.50 ppm and 3.70-3.80 ppm correlate to the carbon (C6) at 44.3 ppm and were assigned based on deshielding effects caused by adjacent nitrogen. The rest of the methylene protons are overlapping between 1-2.5 ppm and are difficult to correlate to their corresponding carbons.

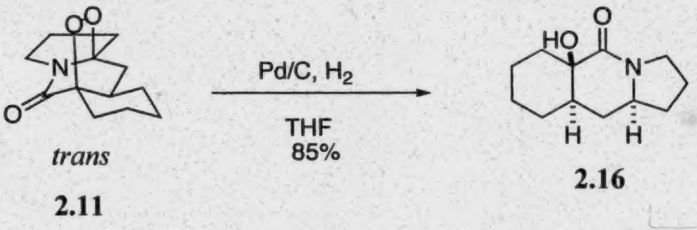
2.7 Peroxy-Bridge Reduction

In order to demonstrate the utility of this methodology in natural product synthesis, we decided to attempt reduction of the peroxide functionality to provide indolizidinone structures. Various conditions were employed and finally the peroxide reduction was accomplished by Pd/C hydrogenation at room temperature and atmospheric pressure. This reduction process furnished indolizidinone structures bearing an α-hydroxy group (Scheme 2.17). In the case of substrates **2.8a** and **2.10,** the reduction resulted in bicyclic amides bearing an α-hydroxy substituent along with an olefinic functionality. The products were characterized via NMR and IR spectroscopy but these products were unstable after purification, which made it difficult to obtain clean spectra.

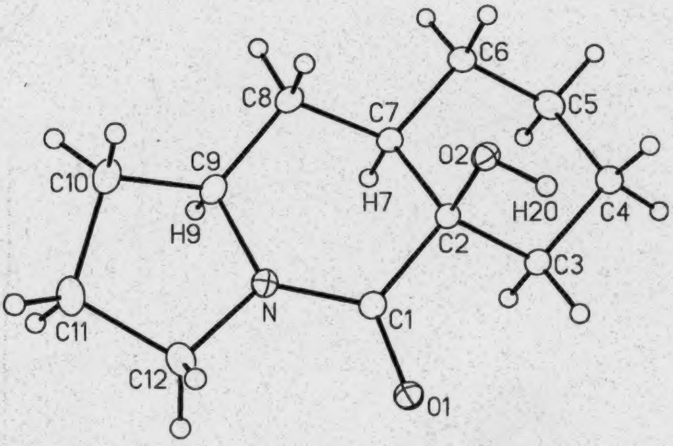


Scheme 2.17 Peroxy-Bridge Reduction for Compounds **2.8a** and **2.10**

In the case of substrate **2.11**, the reduction process resulted in a saturated tricyclic lactam, **2.16** (Scheme 2.18). Fortunately, we were able to obtain an X-ray crystal structure of this compound. Based on the X-ray data, the relative stereochemistry of both substrate and product was established (Scheme 2.19).

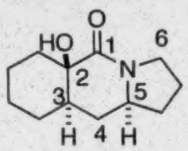

trans
2.11
Pd/C, H2
THF
85%
HO
O
N
H
H
2.16

Scheme 2.18 Peroxy-Bridge Reduction for Compound **2.11**


C6
C5
C8
C7
C10
C9
O2
H7
H20
C4
H9
C2
C3
N
C1
C11
C12
O1

Scheme 2.19 ORTEP for Compound **2.16**

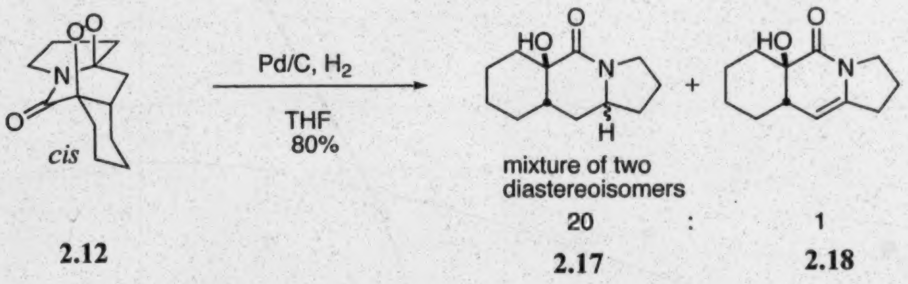
2.7.1 Structure Determination of Tricyclic Compound **2.16**



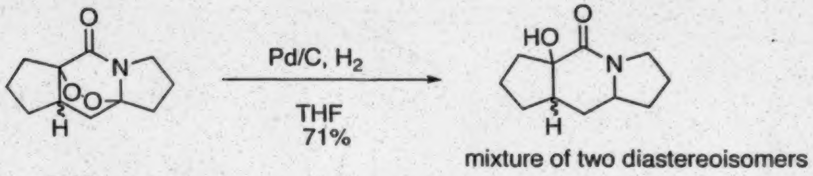
2.16

The electrospray ionization mass spectrum provided the molecular formula of $C_{12}H_{19}NO_2$. The IR spectrum showed a strong absorbance at 1690 cm^{-1} which is a representative of amide carbonyl stretching. IR also showed absorbance at 3276 cm^{-1} which suggests the presence of a hydroxyl group, most likely involved in an internal hydrogen bond. The carbon (C1) at 171.6 ppm was assigned to the amide carbonyl carbon. The carbon at 70.5 ppm is the quaternary carbon bearing the hydroxyl group. The methine proton (H5) at 3.4 ppm correlates with the carbon at 59.8 ppm. Diastereotopic protons at 3.35-3.45 ppm and 3.53 ppm correlate to the carbon (C6) at 44.9 ppm. The rest of methylene protons overlap between 1-2.2 ppm and are difficult to unambiguously assign.

In the case of substrates **2.12** and **2.13a**, reduction of the peroxy bridge resulted in a mixture of products (Scheme 2.20 and 2.21).



Scheme 2.20 Peroxy-Bridge Reduction for Compound **2.12**

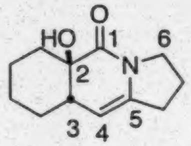


2.13a

2.19

Scheme 2.21 Peroxy-Bridge Reduction for Compound **2.13a**

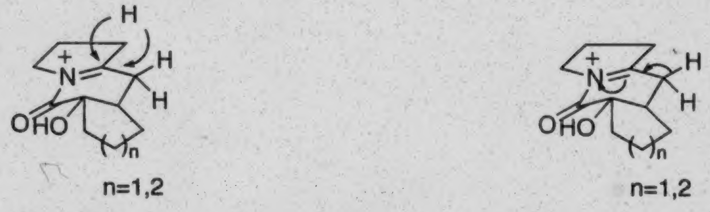
2.7.2 Structure Determination of Tricyclic Compound **2.18**



2.18

The electrospray ionization mass spectrum provided the molecular formula of $C_{12}H_{17}NO_2$. The IR spectrum showed a strong signal at 1641 cm^{-1}, which is a representative of amide carbonyl stretching, and a broad signal at 3382 cm^{-1}, which implies the presence of a hydrogen-bonded hydroxy group. The carbon (C1) at 172.4 ppm was assigned to the amide carbonyl carbon. The carbon at 72.1 ppm is the quaternary carbon bearing the hydroxyl group (C2). Carbons at 102.5 ppm and 139.4 ppm correspond to C4 and C5, respectively. In the HSQC spectrum there was a correlation between C4 and the vinylic proton at 4.75 ppm. Diastereotopic protons at 3.54 ppm and 3.68 ppm correlate to the carbon (C6) at 45.7 ppm.

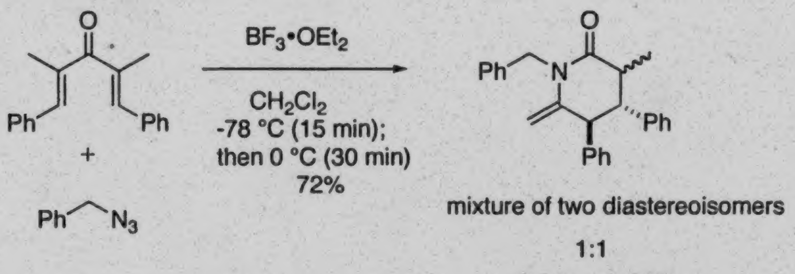
Formation of unsaturated tricyclic amide **2.18** was assumed to be a result of elimination of the α-hydrogen of the resulting iminum ion. Also, the mixture of diastereoisomers obtained from the reduction process in case of compounds **2.17** and **2.19** was a result of two reduction pathways of the iminium intermediate with hydride ion (Scheme 2.22). In the case of substrate **2.19** two diastereoisomers with a ratio of 3:1 were separated and identified by LC-MS.


H
H
H
N
O
HO
n
n=1,2
H
H
N
O
HO
n
n=1,2

Scheme 2.22 Proposed Rational for the Formation of Compounds **2.18** and **2.19**

2.8 Intermolecular Azide Trapping of Dienones

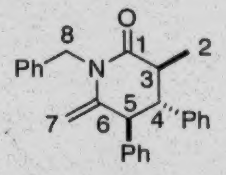
We have also attempted the intermolecular version of the Nazarov cyclization/azide trapping process. We were hoping to obtain six-membered lactams from two simple building blocks. Treating a simple dienone such as dibenzylidenepentanone[16] with a benzyl azide in the presence of BF_3•OEt_2 led to the formation of a piperidinone compound. This intermolecular process showed the high reactivity of the oxyallyl carbocation and the ability of simple organo-azides to trap the cationic species in an intermolecular process (Scheme 2.23).


O
Ph
Ph
+
Ph
N3
BF3•OEt2
CH2Cl2
-78 °C (15 min);
then 0 °C (30 min)
72%
O
Ph
N
Ph
Ph
mixture of two diastereoisomers
1:1

2.20a : 2.20b

Scheme 2.23 Intermolecular Azide Trapping Process

2.8.1 Structure Determination of Piperidinone **2.18a**



2.20a

The electrospray ionization mass spectrum identified the molecular formula as $C_{26}H_{25}NO$. The carbon (C1) at 172.6 ppm was assigned to the amide carbonyl carbon. In the HMQC spectrum, the methyl carbon (C2) at 15.8 ppm, correlates with methyl protons at 1.14 ppm. Carbons at 44.0 ppm, 51.5 ppm, and 53.2 ppm were assigned to C3, C4, and C5, respectively, based on 2D HMQC and COSY spectra. The vinylic carbon (C7) at 97.5 ppm correlates to vinylic protons at 3.77 ppm and 4.50 ppm based on the 2D HMQC spectrum. The two diastereotopic protons at 5.02 ppm and 5.13 ppm are connected to the *N*-benzyl methylene carbon (C8) at 48.2 ppm. The relative stereochemistry at methine carbons C3 and C4 was determined to be *trans* based on the large coupling constant observed between the attached protons (J = 11.6 Hz). The relative *trans* stereochemistry between benzylic methine carbons C4 and C5 was established during conrotatory ring closure of the dienone precursor.

In case the of substrate **2.20b** the relative stereochemistry at methine carbons C3 and C4 similar to substrate **2.20a** was determined to be *cis* based on the small coupling constant observed between the attached protons (J = 5.5 Hz). The structure of compound **2.20b** was determined similar to compound **2.20a** based on 1D and 2D NMR experiments.

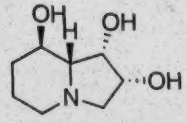
In these two monocyclic lactams absence of the peroxide functionality was noticeable. The lack of peroxide products could be explained by faster rate of protonation/deprotonation of the 1,4-dipole intermediate versus reaction of this reactive intermediate with ambient oxygen.

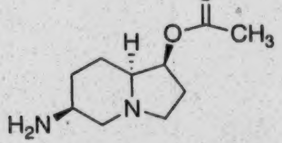
2.9 Future Directions

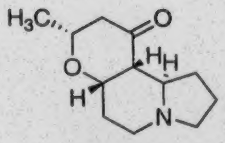
Some questions regarding exploration and future application of the intramolecular azide trapping process remain unanswered. The possible intermediacy of 1,4-dipole intermediate could open doors to investigate the reactivity of these species with either electron-poor or-rich dipolarophiles. Another area for attention is the limitations of the peroxy bridge reduction process. The Pd/C hydrogenation method led to the formation of inseparable mixture of isomers in some of the examples. Examination of other reducing methods such as Ph_3P or mild acid conditions for peroxy-bridge ring opening should be examined.

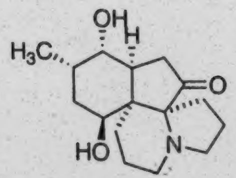
There is a great deal of potential in this chemistry for the rapid construction of polycyclic nitrogen-containing ring systems, which are formed in many important classes of bioactive natural products. Before this sort of application can be initiated, more needs to be learned about the scope and limitations of the process. In the interrupted Nazarov reaction the degree of substitution always were crucial for the initial Nazarov cyclization and stereochemical out come of the reaction. Sometimes the presence of α and β-substitutions is essential for the interrupted Nazarov reaction to proceeds. The Examination of dienones bearing different functional groups like ester, ether, amine and silicon should be considered, since these serve as useful handles in further synthetic manipulations. For example in an indolizidine alkaloid (-)-slaframine there is an amine group in the six-membered ring which could come from a dienone containg a protected α-amino functionality. Also in swainsonine the γ-hydroxy group could be made from a dienone bearing a β-silicon group before oxidation. Examination of the compatibility of these functional groups with the reaction conditions is essential for the further utility of those in natural product synthesis. Elongation the tether length by one carbon could lead to quinolizidine alkaloids. Moreover, installation a tether containing an unsaturation unit could be useful handle for functional group manipulations like dihydroxylation. Last but not least there is one question still remain unanswered which would be application of either chiral auxiliaries or chiral Lewis acids to influence the stereochemical outcome of the reaction.

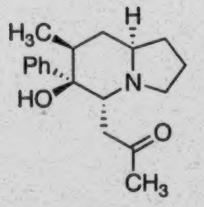
Once these issues have been addressed, it may be feasible to develop an approach to the chemical synthesis of several natural products, particularly those possessing an indolizidine ring system. Among those bicyclic alkaloids bearing a bridgehead nitrogen atom, indolizidine alkaloids, having fused 6/5-ring systems occupy a large number of natural products. Natural products containing this structural motif show a variety of biological activities, from glycosidase inhibition to cardiotonic and myotonic activities.[17] The “domino” intramolecular azide trapping of the Nazarov intermediate could be a very efficient and rapid method of accessing these structures bearing different functional groups. Many of indolizidine natural products like swainsonine, (+)-pumiliotoxin B contain γ-hydroxy groups. Installation of the proper silicon on the dienone bearing a pendant azide group could be an alternative route to these natural products (Scheme 2.25).

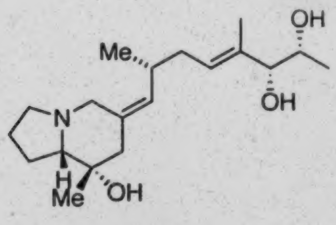

swainsonine


(-)-slaframine


(+)-elaeokanine E

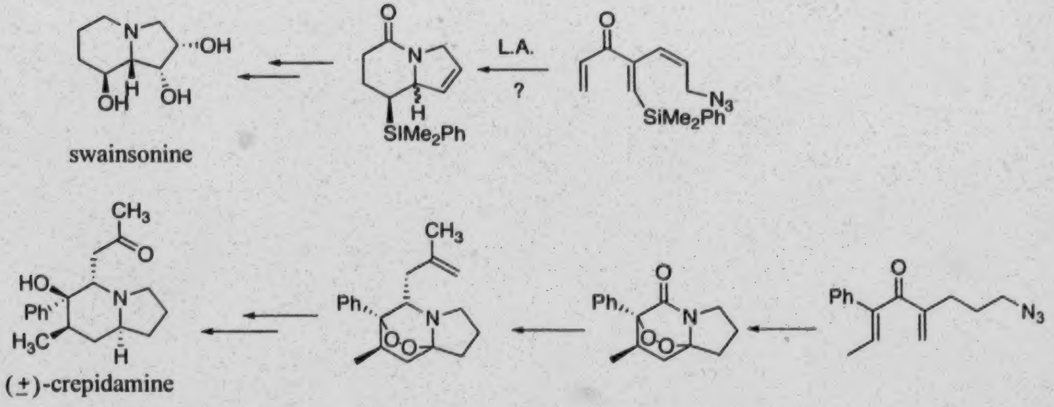

(-)-serratinine


(±)-crepidamine


(+)-pumiliotoxin B

Indolizidine alkaloids

Some of the indolizidine natural products like (±) crepidamine contains an α-hydroxy group which shows the significance of this method to build such a these functionality after the peroxy-bridge reduction. The methyl ketone group could be installed via conversion of the amide functionality to the iminium triflate followed by cuprate addition of 2-bromopropene. The double bond functionality could be converted to the desired ketone after ozonolysis and periodate promoted cleavage (Lemiex-Johnson method).



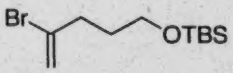
Scheme 2.24 Future Application in Natural Product Synthesis

2.10 Conclusion

In summary, we have developed a novel "domino" Nazarov cyclization/azide trapping process for the construction of complex heterocycles. This interrupted Nazarov reaction has been used to synthesize various functionalized mono- and polycyclic lactams, which could be useful substrates in natural product synthesis. In this process one new carbon-carbon bond, two new carbon-nitrogen bonds and up to three stereogenic centers can be formed in one synthetic step.

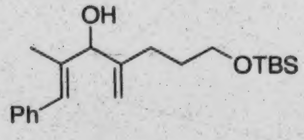
2.11 Experimental Section

General Information. Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, diethylether and benzene from sodium/benzophenone ketyl, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Liquid chromatography-mass spectrometry (LC-MS) was carried out using Agilent-1100 series. Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to tetramethylsilane (0 ppm, ^{1}H; ^{13}C) or to deuteriochloroform (7.26 ppm, ^{1}H; 77.23 ppm, ^{13}C) or to deuteriodicholormethane (5.32 ppm, ^{1}H; 53.8 ppm, ^{13}C) as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz. Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra were determined on a PerSeptive Biosystem Mariner high-resolution electrospray spectrometer in the positive mode.



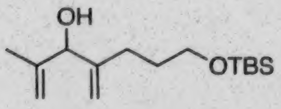
2.1

Preparation of 2.1. To a solution of 4-bromo-4-penten-1-ol[5] (0.40 g, 2.4 mmol), triethylamine (0.37 mL, 2.6 mmol), and 4-(N, N)-dimethylamino pyridine (DMAP) (0.01 g, 0.1 mmol) in CH_2Cl_2 (6 mL) at room temperature was added a solution of TBDMSCl (0.40 g, 2.6 mmol) in CH_2Cl_2 (2 mL). After the addition, the mixture was stirred overnight under argon. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl (3 x 30 mL), water (3 x 30 mL), brine (50 mL), and dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure, the residue was purified with flash chromatography (silica gel; 9:1 hexanes/EtOAc) to give 0.51 g (76%) of the pure silyl ether **2.1** as a colorless oil: R_f 0.80 (20:1 hexanes/EtOAc); IR (neat) 2954, 2929, 2895, 2858, 1471, 1630, 1255, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59-5.56 (m, 1H), 5.41-5.39 (m, 1H), 3.63 (t, 2H, $J = 6.1$ Hz), 2.50 (t, 2H, $J = 7.6$ Hz), 1.79-1.74 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 116.5, 61.4, 37.8, 30.9, 25.8, 18.2, -5.3; HRMS calcd for $C_{10}H_{20}OSiBr$ (M^+-OCH_3) 263.0466, found: *m/z* 263.0464; Anal. Calcd for $C_{11}H_{23}BrOSi$: C, 47.30; H, 8.30. Found: C, 47.77; H, 8.39.



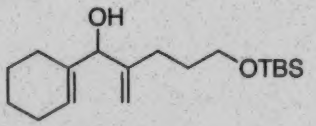
2.2a

Preparation of 2.2a. To a stirred solution of silyl ether **2.1** (3.9 g, 14 mmol) in THF (35 mL) was added *t*-BuLi (18.9 mL, 1.7 M in pentane, 32.2 mmol) over 15 min. at -78 °C, under argon. After 30 min; α-methyl-*trans*-cinnamaldehyde (2.3 mL, 16 mmol) was added dropwise and the reaction mixture was allowed to stir for 3 hours at room temperature before being quenched by the addition of saturated NH_4Cl solution (50 mL) at -78 °C. After warming to room temperature the aqueous layer was extracted with Et_2O (2 x 100 mL) and the combined ethereal fractions were washed with saturated NH_4Cl solution (100 mL) and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash chromatography (silica gel; 20:1 hexanes/ethyl acetate) to give 3.02 g (63%) of the pure dienol **2.2a** as a yellow oil: R_f 0.20 (20:1 hexanes/EtOAc); IR (neat) 3408, 2953, 2929, 2857, 1471, 1255, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 6.62 (br s, 1H), 5.20 (br s, 1H), 5.02-4.98 (m, 1H), 4.6 (s, 1H), 3.62 (t, 2H, J = 6.2 Hz), 2.15-1.95 (m, 3H), 1.78-1.65 (m, 2H), 1.75 (d, 3H, J = 1.3 Hz), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.0, 137.7, 129.0, 128.1, 126.7, 126.4, 110.8, 80.6, 62.8, 31.2, 28.1, 25.9, 18.3, 13.6, -5.2; HRMS (ESI) [M^+] for $C_{21}H_{34}O_2Si$ calcd 346.2328, found: *m/z* 346.2319; Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.78; H, 9.89. Found: C, 71.83; H, 9.83.



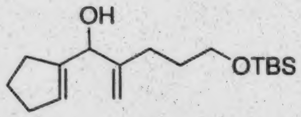
2.2b

Preparation of 2.2b. Dienol **2.2b** was prepared from methacrolein in 63% yield as a yellow oil by following the procedure for the preparation of **2.2a**. R_f 0.43 (silica gel; 9:1 hexanes/EtOAc); IR (neat) 3428, 2953, 2929, 2857, 1471, 1255, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (br s, 1H), 5.08-5.04 (m, 1H), 4.94-4.92 (m, 1H), 4.92-4.89 (m, 1H), 4.48 (s, 1H), 3.60 (t, 2H, *J* = 6.3 Hz) 2.10-1.90 (m, 3H), 1.72-1.63 (m, 2H), 1.62 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.0, 111.7, 110.6, 78.9, 62.6, 31.0, 27.4, 25.8, 18.1, 17.7, -5.4; HRMS (ESI) $[M+Na]^+$ for $C_{15}H_{30}O_2SiNa$ calcd 293.1907, found: *m/z* 293.1907; Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.69; H, 11.12.



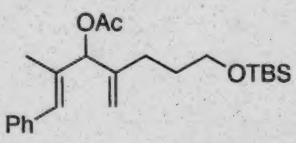
2.2c

Preparation of 2.2c. Dienol **2.2c** was prepared from cyclohex-1-enecarbaldehyde in 65% yield as a yellow oil by following the procedure for the preparation of **2.2a**. R_f 0.37 (20:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (app ttd, 1H, *J* = 3.7, 1.7, 1.0 Hz), 5.09 (app tt, 1 H, *J* = 1.5, 0.8 Hz), 4.91 (app qd, 1H, *J* = 1.4, 1.0 Hz), 4.40 (s, 1H), 3.62 (t, 2H, *J* = 6.3 Hz), 2.10-1.50 (m, 12H), 0.90 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 137.6, 124.0, 109.5, 79.1, 62.7, 31.0, 28.0, 25.8, 24.9, 23.5, 22.5, 22.4, -5.4; HRMS (ESI) $[M+Na]^+$ for $C_{18}H_{34}O_2SiNa$ calcd 333.2220, found: m/z 333.2218. (The TBS-quaternary carbon was not detected in the ^{13}C NMR spectrum).



2.2d

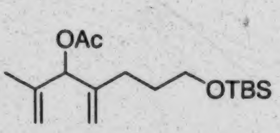
Preparation of 2.2d. Dienol **2.2d** was prepared from cyclopent-1-enecarbaldehyde in 71% yield as a yellow oil by following the procedure for the preparation of **2.2a**. R_f 0.37 (20:1 hexanes/EtOAc); IR (neat) 3426, 2953, 2894, 2857, 1255, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68-5.65 (m, 1H), 5.09-5.07 (m, 1H), 4.91-4.88 (m, 1H), 4.65 (br s, 1H), 3.62 (t, 2H, $J = 6.2$ Hz), 2.40-2.30 (m, 2H), 2.24-2.12 (m, 2H), 2.11-1.80 (m, 4H), 1.70-1.60 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 144.8, 126.3, 109.9, 74.8, 62.7, 32.2, 31.3, 31.0, 27.6, 25.8, 23.2, 18.1, -5.4; HRMS (ESI) $[M+Na]^+$ for $C_{17}H_{32}O_2Si$ Na: calcd 319.2063, found: *m/z* 319.2064; Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.02; H, 10.92.



2.3a

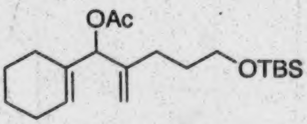
Preparation of 2.3a. To a solution of the alcohol **2.2a** (0.41g, 1.1 mmol), and DMAP (0.007 g, 0.05 mmol) in pyridine (4 mL) was added Ac_2O (0.56 mL, 5.9 mmol). After stirring at room temperature for 10 h, the reaction mixture was quenched by addition of 5% HCl (2 x 50 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic fractions were washed with brine (50 mL) and dried over

$MgSO_4$. The crude product was purified by flash chromatography (silica gel; 20:1 hexanes/EtOAc) to give 0.36 g (78%) of the pure ester **2.3a** as a yellow oil: R_f 0.40 (9:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.20 (m, 5H), 6.57 (br s, 1H), 5.68 (br s, 1H), 5.12 (br s, 1H), 5.01-4.99 (m, 1H), 3.62 (t, 2H, *J* = 6.3 Hz), 2.12 (s, 3H), 2.12-2.04 (m, 2H), 1.80 (d, 3H, *J* = 1.4 Hz), 1.78-1.66 (m, 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.3, 137.1, 134.2, 128.9, 128.6, 128.0, 126.6, 111.2, 80.9, 62.5, 30.8, 28.5, 25.8, 21.2, 18.2, 13.8, -5.3; HRMS (ESI) $[M+Na]^+$ for $C_{23}H_{36}O_3Si$ Na: calcd 411.23260, found: *m/z* 411.2323.



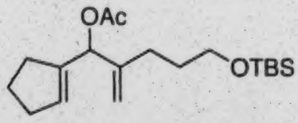
2.3b

Preparation of 2.3b. Ester **2.3b** was prepared in 96% yield as a yellow oil by following the procedure for the preparation of **2.3a**. R_f 0.40 (20:1 hexanes/EtOAc), IR (neat) 2953, 2929, 2857, 1744, 1371, 1235, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (br s, 1H), 5.06-5.04 (m, 1H), 5.02-5.00 (m, 1H), 4.96-4.92 (m, 2H), 3.59 (t, 2H, *J* = 6.3 Hz), 2.10-1.96 (m, 2H), 2.06 (s, 3H), 1.71-1.60 (m, 2H), 1.64 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.0, 141.3, 113.4, 111.6, 79.4, 62.5, 30.7, 27.9, 25.8, 21.0, 18.18, 18.16, -5.3; HRMS (ESI) $[M+Na]^+$ for $C_{17}H_{32}O_3SiNa$ calcd 335.2013, found: *m/z* 335.2014; Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.45; H, 10.33.



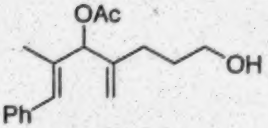
2.3c

Preparation of 2.3c. Ester **2.3c** was prepared in 87% yield as a yellow oil by following the procedure for the preparation of **2.3a**. R_f 0.50 (20:1 hexane/EtOAc); IR (neat) 2929, 2858, 1743, 1472, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76-5.72 (m, 1H), 5.50-5.47 (m, 1H), 5.01-4.99 (m, 1H), 4.91 (app qd, 1H, *J* = 1.4, 1.2 Hz), 3.60 (t, 2H, *J* = 6.3 Hz), 2.07 (s, 3H), 2.04-1.96 (m, 4H), 1.90-1.84 (m, 2H), 1.70-1.50 (m, 6H), 0.90 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 145.7, 134.2, 126.0, 110.5, 79.9, 62.6, 30.8, 28.5, 25.9, 25.0, 24.1, 22.4, 22.2, 21.2, 18.2, -5.2; HRMS (ESI) $[M+Na]^+$ for $C_{20}H_{36}O_3SiNa$: calcd 375.2326, found: *m/z* 375.2327; Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 67.72; H, 10.35.



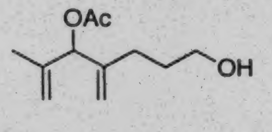
2.3d

Preparation of 2.3d. Ester **2.3d** was prepared in 78% yield as a yellow oil by following the procedure for the preparation of **2.3a**. R_f 0.77 (9:1 hexanes/EtOAc); IR (neat) 2953, 2929, 2856, 1743, 1235 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (br s, 1H), 5.66-5.65 (m, 1H), 5.06-5.04 (m, 1H), 4.94-4.92 (m, 1H), 3.62 (t, 2H, *J* = 6.3 Hz), 2.40-2.30 (m, 2H), 2.26-2.18 (m, 2H), 2.08 (s, 3H), 2.08-2.00 (m, 2H), 1.90-1.80 (m, 2H), 1.70-1.60 (m, 2H), 0.90 (s, 9H), 0.01 (s, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 145.8, 141.0, 128.2, 111.1, 75.7, 62.6, 32.3, 31.7, 30.8, 28.2, 25.9, 23.1, 21.1, 18.2, -5.3; HRMS (ESI) $[M+Na]^+$ for $C_{19}H_{34}O_3Si$ Na: calcd 361.2169, found: *m/z* 361.2169; Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.56; H, 10.09.



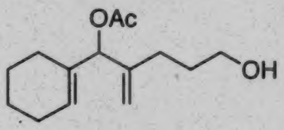
2.4a

Preparation of 2.4a. A solution of AcOH/H_2O/THF (3:1:1) was added to a flask containing (0.045 g, 0.11 mmol) of ester **2.3a**. The reaction mixture was allowed to stir for 6 h at room temperature. The mixture was diluted with 10 mL of Et_2O and washed with saturated aqueous $KHCO_3$ (3 x 20 mL), water (20 mL), and the combined organic layer dried over $MgSO_4$. The residue was purified by flash chromatography (silica gel; 7:3 hexanes/EtOAc) to give 0.028 g (88 %) of the pure alcohol **2.4a** as a yellow oil: R_f 0.37 (7:3 hexanes/EtOAc), IR (CH_2Cl_2, cast film) 3419, 3023, 2939, 1738, 1235 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 6.60 (br s, 1H), 5.70 (br s, 1H), 5.16 (br s, 1H), 5.05-5.03 (m, 1H), 3.67 (t, 2H, J = 6.4 Hz), 2.16-2.09 (m, 2H), 2.12 (s, 3H), 1.84-1.80 (m, 2H), 1.82 (d, 3H, J = 1.3 Hz), 1.72 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 145.0, 137.0, 134.1, 128.9, 128.7, 128.1, 126.8, 111.7, 80.9, 62.3, 30.6, 28.6, 21.2, 13.9; HRMS (EI) $[M^+]$ for $C_{17}H_{22}O_3$ calcd 274.1568, found: *m/z* 274.1560.



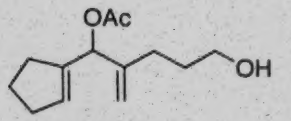
2.4b

Preparation of 2.4b. Ester **2.4b** was prepared in 73% yield as an oil by following the procedure for the preparation of **2.4a**. R_f 0.33 (7:3 hexanes/ EtOAc 7:3), IR (neat) 3426, 2941, 2874, 1741, 1647, 1373, 1236 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (br s, 1H), 5.14 (br s, 1H), 5.00 (br s, 1H), 5.03 (br s, 1H), 5.06 (br s, 1H), 3.66 (t, 2H, J = 6.4 Hz), 2.16-2.04 (m, 3H), 2.14 (s, 3H), 1.82-1.74 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 169.8, 144.8, 141.3, 113.6, 112.1, 79.4, 62.3, 30.6, 28.0, 21.1, 18.2; HRMS (ESI) [M+Na]$^+$ for $C_{11}H_{18}O_3Na$ calcd 221.1148, found: *m/z* 221.1148; Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.36; H, 9.22.



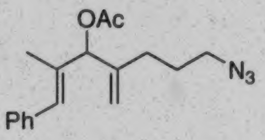
2.4c

Preparation of 2.4c. Ester **2.4c** was prepared in 82% yield as an oil by following the procedure for the preparation of **2.4a**. R_f 0.20 (8:2 hexanes/EtOAc); IR (neat) 3418, 2930, 1737, 1649, 1437, 1371, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76-5.72 (m, 1H), 5.46 (br s, 1H), 5.02-5.01 (m, 1H), 4.94-4.92 (m, 1H), 3.64 (t, 2H J = 6.3 Hz), 2.06 (d, 3H J = 0.6 Hz), 2.08-1.98 (m, 4H), 1.90-1.83 (m, 2H), 1.74-1.68 (m, 2H), 1.64-1.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.5, 134.3, 126.4, 111.2, 80.1, 62.6, 30.8, 28.7, 25.2, 24.3, 22.6, 22.4, 21.4; HRMS (ESI) [M+H]$^+$ for $C_{14}H_{22}O_3Na$: calcd 261.1461, found: *m/z* 261.1461; Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.32; H, 9.58.



2.4d

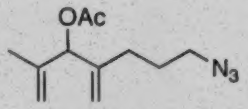
Preparation of 2.4d. Ester **2.4d** was prepared in 78% yield as an oil by following the procedure for the preparation of **2.4a**. R_f 0.20 (8:2 Hexanes/EtOAc); IR (neat) 3420, 2939, 2850, 1740, 1371, 1237, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (br s, 1H), 5.67-5.65 (m, 1H), 5.07-5.06 (m, 1H), 4.96-4.95 (m, 1H), 3.65 (t, 2H, *J* = 6.4 Hz), 2.40-2.30 (m, 2H), 2.26-2.20 (m, 2H), 2.08 (s, 3H), 2.12-2.00 (m, 2H), 1.90-1.82 (m, 2H), 1.76-1.70 (m, 2H), 1.64 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 145.4, 140.9, 128.4, 111.5, 75.6, 62.3, 32.3, 31.7, 30.6, 28.2, 23.1, 21.1; HRMS (ESI) $[M+Na]^+$ for $C_{13}H_{20}O_3Na$: calcd 247.13047, found: *m/z* 247.13044; Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 68.75; H, 8.80.



2.5a

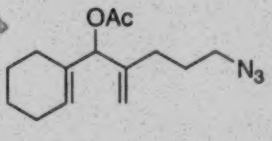
Preparation of 2.5a. A solution of ester **2.4a** (0.096 g, 0.34 mmol) in THF (4 mL) was added to a solution of triphenylphosphine (0.10 g, 0.40 mmol), DIAD (0.08 g, 0.4 mmol) in THF (10 mL). After 2 min a white precipitate formed and a solution of diphenylphosphoryl azide[8b] (0.11 g, 0.40 mmol) in THF (4 mL) was added. The mixture was stirred for 10 hours, and then concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel; 30:1 hexanes/EtOAc) to afford 0.090 g (85%) of the azide **2.5a** as a yellow oil: R_f 0.70 (7:3 hexanes/EtOAc); IR (neat)

2943, 2097, 1739, 1235 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.24 (m, 5H), 6.59 (br s, 1H), 5.68 (br s, 1H), 5.19 (br s, 1H), 5.08-5.02 (m, 1H), 3.31 (app td, 2H J = 6.7, 2.1 Hz), 2.18-2.10 (m, 2H), 2.14 (s, 3H), 1.84-1.80 (m, 2H), 1.82 (d, 3H, J = 1.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.8, 144.5, 137.2, 134.2, 129.2, 129.0, 128.4, 127.1, 112.6, 81.0, 51.1, 29.6, 27.2, 21.4, 14.1; HRMS (ESI) [M+Na]$^+$ for $C_{17}H_{21}N_3O_2Na$ calcd 322.1526, found: *m/z* 322.1526; Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 10.69. Found: C, 68.48; H, 7.13; N, 12.9.



2.5b

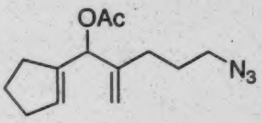
Preparation of 2.5b. Azide **2.5b** was prepared in 70% yield as a yellow oil by following the procedure for the preparation of **2.5a**. R_f 0.80 (7:3 hexanes/EtOAc), IR (neat) 2944, 2098, 1741, 1236 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.54 (br s, 1H), 5.13 (br s, 1H), 5.06-5.02 (m, 1H), 5.02-4.96 (m, 2H), 3.29 (t, 2H, J = 7.7 Hz) 2.12-2.02 (m, 2H), 2.10 (s, 3H), 1.76 (app quint, 2H, J = 7.3 Hz), 1.67 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.9, 144.2, 141.4, 113.9, 113.0, 79.4, 51.1, 29.0, 27.1, 21.3, 18.4; HRMS (ESI) [M+Na]$^+$ for $C_{11}H_{17}N_3O_2Na$ calcd 246.1213, found: *m/z* 246.1214; Anal. Calcd for $C_{11}H_{17}N_3O_2$ C, 59.17; H, 7.67; N, 18.82. Found: C, 59.41; H, 7.71; N, 17.75.



2.5c

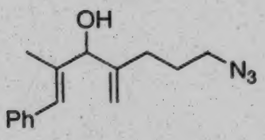
Preparation of 2.5c. Azide **2.5c** was prepared in 90% yield as a yellow oil by following the procedure for the preparation of **2.5a**. R_f 0.75 (7:3 hexanes/EtOAc); IR

(neat) 2931, 2859, 2099, 1776, 1742, 1370, 1240 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ5.75 (app ttd, 1H, *J* = 3.7, 1.7, 1.0 Hz), 5.46 (br s, 1H), 5.04 (br s, 1H), 4.94-4.92 (m, 1H), 3.30 (app td, 2H, *J* = 6.8, 1.9 Hz,), 2.10-2.00 (m, 4H), 2.07 (s, 3H), 1.90-1.84 (m, 2H), 1.80-1.70 (m, 2H, *J* = 7.1, 6.8 Hz), 1.65-1.45 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7, 144.4, 133.8, 126.1, 111.5, 79.5, 50.7, 29.2, 26.8, 24.9, 23.9, 22.3, 22.1, 21.0; HRMS (ESI) [M+Na]$^+$ for $C_{14}H_{21}N_3O_2Na$: calcd 286.1526, found: *m/z* 286.1526; Anal. Calcd for $C_{14}H_{21}N_3O$: C, 63.85; H, 8.04; N, 15.96. Found: C, 64.64; H, 8.15, N, 15.85.



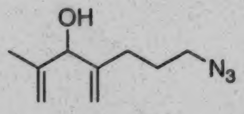
2.5d

Preparation of 2.5d. Azide **2.5d** was prepared in 73% yield as a yellow oil by following the procedure for the preparation of **2.5a**. R$_f$ 0.9 (7:3 hexanes/EtOAc); IR (neat) 2937, 2097, 1740, 1236 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.74 (br s, 1H), 5.68-5.66 (m, 1H), 5.11-5.09 (m, 1H), 4.96-4.94 (m, 1H), 3.28 (t, 2H, *J* = 6.7 Hz), 2.40-2.30 (m, 2H), 2.26-2.20 (m, 2H), 2.08 (s, 3H), 2.12-2.00 (m, 2H), 1.92-1.84 (m, 2H), 1.80-1.72 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.1, 144.9, 141.1, 128.7, 112.5, 75.7, 51.1, 32.6, 32.0, 29.3, 27.2, 23.4, 21.3; HRMS (ESI) [M+Na]$^+$ for $C_{13}H_{19}N_3O_2Na$: calcd 272.1369, found: *m/z* 272.1372; Anal. Calcd for $C_{13}H_{19}$ N_3O_2: C, 62.63; H, 7.68; N, 16.85; Found: C, 62.45; H, 7.69; N, 15.83.



2.6a

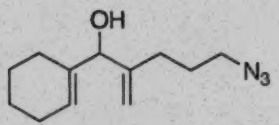
Preparation of 2.6a. To a solution of acetate **2.5a** (0.11 g, 0.36 mmol) in dry methanol (4 mL), was added anhydrous potassium carbonate (0.056 g, 0.46 mmol). The resulting white suspension was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane and passed through a short pad of silica gel, with suction. Further elution with dichloromethane, followed by ethyl acetate, and subsequent evaporation of the solvent afforded 0.079 g (85%) of the crude alcohol **2.6a** as a yellow oil, used without further purification: R_f 0.22 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 6.63 (br s, 1H), 5.30-5.26 (m, 1H), 5.06-5.02 (m, 1H), 4.64 (s, 1H), 3.20 (app td, 2H, J = 6.8, 1.9 Hz), 2.11 (m, 2H), 1.84-1.78 (m, 2H), 1.80 (d, 3H, J = 1.3 Hz), 1.60 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 137.7, 137.3, 128.9, 128.1, 127.0, 126.6, 111.3, 80.4, 51.0, 28.9, 27.2, 13.4.



2.6b

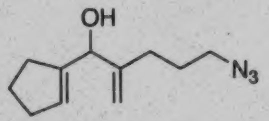
Perparation of 2.6b. Dienol **2.6b** was prepared in 82% yield as a yellow oil by following the procedure for the preparation of **2.6a**. The crude material carried through the next step. R_f 0.30 (9:1 hexanes/EtOAc), IR (neat) 3417, 2942, 2098, 1645, 1450, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.16 (m, 1H), 5.08-5.06 (m, 1H), 4.98-4.93 (m, 2H), 4.50 (s, 1H) 3.27 (t, 2H, J = 6.8 Hz), 2.12-1.94 (m, 2H), 1.80-1.66 (m, 3H), 1.63

(app t, 3H, J = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 145.2, 112.4, 111.6, 79.1, 51.3, 28.5, 27.4, 17.9.



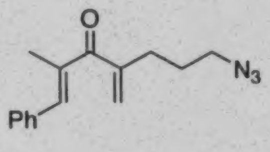
2.6c

Preparation of 2.6c. Dienol **2.6c** was prepared in 79% yield as a yellow oil by following the procedure for the preparation of **2.6a**. The crude material carried through the next step. R_f 0.65 (7:3 hexanes/EtOAc); IR (neat) 3400, 2928, 2857, 2103, 1448, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (app ttd, 1H, J = 3.7, 1.7, 1.0 Hz), 5.14 (app tt, 1H, J = 1.5, 0.8 Hz) 4.93-4.91 (m, 1H), 4.40 (s, 1H), 3.26 (app td, 2H, J = 6.8, 1.1 Hz), 2.10-1.90 (m, 5H), 1.82-1.66 (m, 4H), 1.62-1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.8, 124.7, 110.7, 79.3, 51.2, 29.1, 27.4, 25.3, 23.8, 22.8, 22.7; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{19}N_3ONa$: calcd 244.1420, found: *m/z* 244.1420.



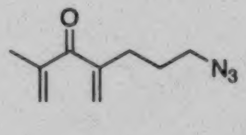
2.6d

Preparation of 2.6d. Dienol **2.6d** was prepared in 89% yield as a yellow oil by following the procedure for the preparation of **2.6a**. The crude material carried through the next step. R_f 0.55 (7:3 hexanes/EtOAc); IR (cast film) 3400, 2943, 2936, 2100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.68 (m, 1H), 5.15-5.13 (m, 1H), 4.93-4.92 (m, 1H), 4.71 (br s, 1H), 3.28 (t, 2H, *J* = 7.0 Hz), 2.40-2.30 (m, 2H), 2.30-2.18 (m, 2H), 2.14-1.98 (m, 3H), 1.92-1.80 (m, 2H), 1.70-1.80 (m, 2H).



2.7a

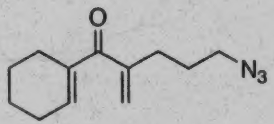
Preparation of 2.7a. To a solution of Dess-Martin periodinane (0.15 g, 0.36 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (0.15 g, 1.8 mmol). The resulting mixture was stirred for 5 min, and then a solution of crude alcohol **2.6a** (0.079 g, 0.30 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. Stirring was continued for another 30 min and the reaction mixture was poured onto a silica gel plug, which was washed and eluted with CH_2Cl_2 (100 mL). The filtrate was concentrated and the crude material purified by flash chromatography (silica gel; 8:2 hexanes/EtOAc) to give 0.067 g (86 %) of the pure dienone **2.7a** as a yellow oil: R_f 0.7 (6:4 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5H), 7.30 (br s, 1H), 5.70 (br s, 1H), 5.64 (br s, 1H), 3.35 (t, 2H, *J* = 6.8 Hz), 2.50 (t, 2H, *J* = 7.6 Hz), 2.16 (s, 3H) 1.80 (app quint, 2H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 147.1, 141.0, 137.1, 135.9, 129.9, 128.8, 128.7, 123.4, 51.2, 30.4, 27.7, 14.3.



2.7b

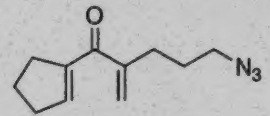
Preparation of 2.7b. Dienone **2.7b** was prepared in 92% yield as a yellow oil by following the procedure for the preparation of **2.7a**. R_f 0.73 (6:4 hexanes/EtOAc), IR

(neat) 2930, 2874, 2097, 1708, 1652, 1450 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.71-5.68 (m, 1H), 5.65-5.60 (m, 3H), 3.24 (t, 2H, *J* = 6.8 Hz), 2.38 (t, 2H, *J* = 7.5 Hz), 1.91-1.88 (m, 3H), 1.72-1.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 199.6, 146.5, 143.9, 125.6, 124.6, 51.0, 29.6, 27.6, 18.5; HRMS (ESI) [M+Na]$^+$ for $C_9H_{13}N_3ONa$ calcd 202.0950, found: *m/z* 202.0952; Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.30; H, 7.26; N, 22.08.



2.7c

Preparation of 2.7c. Dienone **2.7c** was prepared by in 86% yield as a yellow oil following the procedure for the preparation of **2.7a**. R*f* 0.33 (20:1 hexanes/EtOAc); IR (neat) 2934, 2096, 1636, 1285 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.84 (app tt, 1H, *J* = 3.8, 1.5 Hz), 5.56 (app q, 1H, *J*= 1.2 Hz), 5.48 (s, 1H), 3.30 (t, 2H, *J* = 6.8 Hz), 2.40 (t, 2H, *J* = 7.8 Hz), 2.30-2.20 (m, 4H), 1.80-1.60 (m, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.3, 146.6, 142.2, 138.6, 122.0, 50.9, 30.0, 27.4, 26.0, 23.6, 21.9, 21.6; HRMS (ESI) [M+Na]$^+$ for $C_{12}H_{17}N_3ONa$: calcd 242.1263, found: *m/z* 242.1265; Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.83; H, 8.08, N, 19.71.



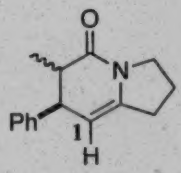
2.7d

Preparation of 2.7d. Dienone **2.7d** was prepared in 82% yield as a yellow oil by following the procedure for the preparation of **2.7a**. R*f* 0.30 (20:1 hexanes/EtOAc); IR

(cast film) 2954, 2096, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (app tt, 1H, *J* = 2.6, 1.7 Hz), 5.69-5.67 (m, 1H), 5.63-5.61 (m, 1H), 3.29 (t, 2H, *J* = 6.8 Hz), 2.64-2.54 (m, 4H), 2.00-1.90 (m, 2H), 1.80-1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 147.9, 145.6, 144.7, 123.1, 51.1, 34.3, 31.8, 29.8, 27.7, 22.9; HRMS (ESI) $[M+Na]^+$ for $C_{11}H_{15}N_3ONa$: calcd 228.1107, Found: *m/z* 228.1109.

Cyclization of 2.7a. To a solution of dienone **2.7a** (149 mg, 0.58 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added anhydrous BF_3•OEt_2 (0.29 mL, 2.3 mmol). After 15 min, the temperature of the reaction mixture was warmed to 0 °C and stirred for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was then added and the reaction was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were concentrated to provide a mixture of three products **2.8a**, **2.8b**, and **2.9**. The three products were then isolated and purified by flash column chromatography (silica gel; 7:3 hexanes/EtOAc) to give 10 mg of **2.9** as a colorless oil, 48 mg of **2.8a**, and 50 mg of **2.8b** as white solids in 70% yield. **2.9/2.8a/2.8b**=1:5:5 (determined by weighing each isomer after purification).

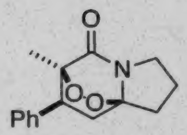
Cyclization of 2.7a under rigorous deoxygenating conditions. Schlenck technique was used to exclude the air oxygen from the reaction media. In two separate 25 mL round bottom flasks, solutions of dienone **2.7a** (9.0 mg, 0.035 mmol) in CH_2Cl_2 (5 mL) and anhydrous BF_3•OEt_2 (0.0088 mL, 0.070 mmol) in CH_2Cl_2 (5 mL) were purged with argon at -78 °C for 30 minutes. The BF_3•OEt_2 solution was then transferred dropwise via cannula to the flask containing the dienone **2.7a**. After 15 min, the temperature of the reaction mixture was warmed to 0 °C and stirred for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was then added and the reaction was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were concentrated to provide **2.9** as the major product. The crude product was purified by flash chromatography (silica gel; 7:3 hexanes/EtOAc) to give 5.6 mg (71%) of **2.9** as an inseparable mixture. Major isomer/minor isomer = 5:1 (determined by integration of HC(1) ^{1}H NMR signals).



2.9

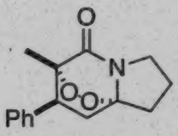
2.9 (major isomer): R_f 0.30 (6:4 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.10 (m, 5H), 5.10 (app dt, 1H, J = 4.7, 1.7 Hz), 3.78-3.66 (m, 3H), 2.88-2.81 (app quin, 1H, J = 7.1 Hz), 2.69-2.63 (m, 2H), 2.01-1.93 (m, 2H), 0.93 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 140.4, 140.0, 128.4, 128.1, 126.7, 100.36, 45.3, 44.2, 40.9, 29.4, 22.3, 11.8; HRMS (ESI) $[M+H]^+$for $C_{15}H_{18}NO$: calcd 228.1382, Found: *m/z* 228.1379.

Partial data for 2.9 (minor isomer): R_f 0.30 (6:4 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.10 (m, 5H), 4.91-3.89 (m, 1H), 3.78-3.66 (m, 3H), 3.40-3.33 (m, 1H), 3.01-2.94 (m, 1H), 2.62-2.55 (m, 2H), 1.18-1.14 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 144.1, 139.2, 128.5, 127.6, 126.6, 100.31, 47.0, 45.2, 43.0, 22.2, 15.2; HRMS (ESI) $[M+H]^+$for $C_{15}H_{18}NO$: calcd 228.1382, Found: *m/z* 228.1379.



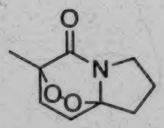
2.8a

2.8a: white solid; R_f 0.26 (6:4 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5H), 4.02-3.96 (m, 1H), 3.70 (ddd, 1H, *J* = 7.3, 5.8, 3.6 Hz), 3.52 (dd, 1H, *J* = 10.1, 4.9 Hz), 2.84 (dd, 1H, *J* = 13.4, 10.1 Hz), 2.30-2.10 (m, 4H), 1.89 (dd, 1H, *J* = 13.0, 5.0 Hz), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 139.8, 128.9, 127.9, 127.5, 95.0, 82.8, 47.0, 45.0, 38.8, 34.6, 23.1, 14.9; HRMS (ESI) $[M+Na]^+$ for $C_{15}H_{17}NO_3$ calcd 282.1100 Found: *m/z* 282.1101.



2.8b

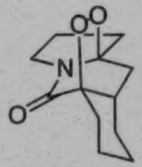
2.8b: white solid; R_f 0.10 (6:4 hexanes/EtOAc); IR (neat) 1686, 1420 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.24 (m, 5H), 3.90 (ddd, 1H, *J* = 11.5, 7.3, 5.0 Hz), 3.62-3.56 (m, 1H), 3.18 (dd, 1H, *J* = 11.5, 5.5 Hz), 2.46 (dd, 1H, *J* = 13.5, 5.4 Hz), 2.37 (dd, 1H, *J* = 13.5, 11.5 Hz), 2.30-2.10 (m, 3H), 2.06-1.99 (m, 1H), 1.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 138.9, 129.1, 128.5, 127.4, 95.2, 82.1, 44.8, 44.4, 38.4, 34.6, 23.1, 14.4; HRMS (ESI) $[M+Na]^+$ for $C_{15}H_{17}NO_3$ Na: calcd 282.1100, Found: *m/z* 282.1100.



2.10

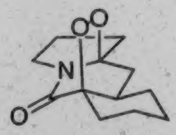
Cyclization of 2.7b. Tricyclic **2.10** was prepared as a white solid in 69% yield by following the procedure for the cyclization of **2.7a**. R_f 0.15 (6:4 hexanes/EtOAc); IR (neat) 2991, 2963, 2940, 2902, 1690, 1253, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90-3.80 (m 1H), 3.50 (app dt, 1H, J = 11.7, 6.5 Hz), 2.38-2.20 (m, 2H), 2.14-2.02 (m, 3H), 2.00-1.90 (m, 2H), 1.80 (app td, 1H, J = 11.5, 2.4 Hz), 1.36 (d, 3H, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 95.5, 79.6, 44.9, 34.7, 29.4, 29.3, 23.3, 16.5; HRMS (ESI) $[M+H]^+$ for $C_9H_{14}NO_3$: calcd 184.0968, found: *m/z* 184.0968; Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.19; H, 7.24; N, 7.41.

Cyclization of 2.7c. 2.11 and **2.12** were prepared in 60% yield as white solids by following the procedure for the cyclization of **2.7a**; **2.12/2.11** = 2:1 (determined by weighing each isomer after purification).



2.12

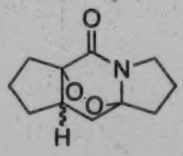
2.12: white solid; R_f 0.33 (6:4 hexanes/EtOAc); mp 63-65 ° C; IR (neat) 2931, 1697, 1420 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88-3.78 (m, 1H), 3.50-3.40 (m, 1H), 2.48 (dd, 1H J = 12.6, 9.7 Hz), 2.22-2.14 (m, 1H), 2.1-1.9 (m, 5H), 1.88-1.78 (m, 2H), 1.76-1.64 (m, 2H), 1.36-1.16 (m, 3H), 1.05 (app dq, 1H, J = 13.1, 3.5 Hz,); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 167.5, 95.9, 82.0, 44.9, 38.0, 36.7, 35.0, 32.5, 27.5, 25.5, 23.8, 23.4; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{17}NO_3Na$: calcd 246.1100, found: *m/z* 246.1102; Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.21; H, 7.82, N, 6.08.



2.11

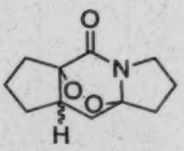
2.11: white solid; R_f 0.22 (6:4 hexanes/EtOAc); mp 59-60 °C; IR (neat) 2933, 1698, 1418 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 3.80-3.70 (m, 1H), 3.50-3.40 (m, 1H), 2.20-1.70 (m, 12H), 1.68-1.54 (m, 1H), 1.50-1.38 (m, 1H), 1.28-1.12 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.6, 95.0, 79.7, 44.7, 37.5, 34.8, 34.6, 29.4, 26.4, 24.8, 23.2, 20.6; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{17}NO_3Na$: calcd 246.1100, found: *m/z* 246.1102.

Cyclization of 2.7d. 2.13a and **2.13b** were prepared in 38% yield as colorless oils by following the procedure for the cyclization of **2.7a**.



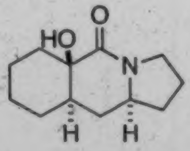
2.13a

2.13a: Mixture of isomers; HRMS (ESI) $[M+H]^+$ for $C_{11}H_{16}NO_3$: calcd 210.1124, found: m/z 210.1125.



2.13b

2.13b: colorless oil; R$_f$ 0.28 (1:1 hexanes/EtOAc); IR (cast film) 2955, 1699, 1412, 916 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.80-3.70 (m, 1H), 3.50-3.40 (m, 1H), 2.34 (ddd, 1H, J = 15.3, 10.8, 4.3 Hz), 2.30-2.20 (m, 1H), 2.10-2.00 (m, 4H), 2.00-2.10 (m, 2H), 1.92-1.64 (m, 4H), 1.48-1.58 (ddd, 1H, J = 15.4, 9.2, 5.6 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.7, 96.9, 90.2, 44.4, 42.6, 34.3, 33.9, 29.9, 25.1, 23.8, 23.4; HRMS (ESI) $[M+H]^+$ for $C_{11}H_{16}NO_3$: calcd 210.11247, found: *m/z* 210.11185.

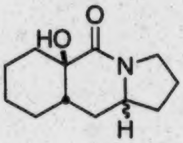


2.16

Preparation of 2.16. Into a 50-mL round bottom flask were placed Pd/C (5 mg, 5 wt.%) and **2.11** (30 mg, 0.12 mmol) in 10 mL of THF. The reaction mixture flushed with argon first then it was hydrogenated for 1h at room temperature and normal pressure (1 atm). The catalyst was removed by filtration via pouring the reaction mixture onto a silica gel plug, which was washed and eluted with CH_2Cl_2 (100 mL). The residue was purified by flash column chromatography (silica gel; 15:1 EtOAc/hexanes) to give 23 mg (85 %) of **2.16** as a white solid. R$_f$ 0.26 (20:1, EtOAc/hexanes); mp 145-147 °C, IR (neat) 3276, 2933, 2858, 1623, 1458 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.53 (app dt, 1H, J = 18.0, 8.9 Hz), 3.45-3.35 (m, 1H), 3.30 (ddd, 1H, J = 12.3, 9.8, 2.2 Hz), 3.00 (br s, 1H), 2.15-

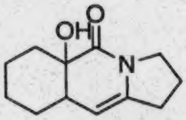
2.22 (m, 1H), 2.02 (q, 1H, *J* = 6.2 Hz), 1.90-1.95 (m, 1H), 1.80-1.70 (m, 3H), 1.68-1.54 (m, 5H), 1.50-1.38 (m, 2H), 1.30-1.20 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 171.6, 70.5, 59.8, 44.9, 42.2, 33.6, 33.3, 30.9, 27.2, 25.9, 22.3, 21.1; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{19}NO_2Na$: calcd 232.1308, found: *m/z* 232.1308.

Preparation of 2.17 and 2.18. 2.17 and **2.18** were prepared from **2.12** in 80% yield by following the procedure for the preparation of **2.16. 2.17/2.18**= 20:1 (determined by weighing each isomer after purification).



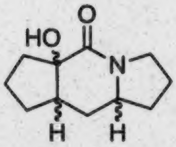
2.17

2.17 (major isomer): white solid; R_f 0.37 (EtOAc); IR (neat) 3363, 2943, 2867, 1622, 1451, 1177 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.50-3.40 (m, 1H), 3.40-3.30 (m, 1H), 3.04 (br s, 1H), 2.19-2.00 (m, 2H), 2.00-1.86 (m, 3H), 1.80-1.20 (m, 11H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 173.8, 72.3, 59.2, 44.6, 38.3, 33.8, 33.7, 31.9, 27.6, 22.6, 21.5, 20.8; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{19}NO_2Na$: calcd 232.1308, found: *m/z* 232.1308.



2.18

2.18: yellow oil; R$_f$ 0.30 (EtOAc); IR (neat) 3382, 2920, 1641, 1057 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.75 (d, 1H, *J* = 1.7 Hz), 3.64 (app dt, 1H, *J* = 14.0, 7.0 Hz), 3.56 (app dt, 1H, *J* = 14.0, 7.0 Hz), 3.32 (s, 1H), 2.70-2.50 (m, 3H), 2.70-1.88 (m, 2H), 1.80-1.40 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 172.4, 139.4, 102.5, 72.1, 45.7, 39.2, 31.8, 29.4, 27.5, 22.9, 21.9, 20.7; HRMS (ESI) [M+Na]$^+$ for $C_{12}H_{17}NO_2Na$: calcd 230.1151, found: *m/z* 246.1150.

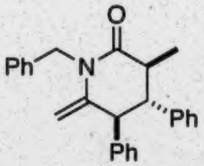


2.19

Preparation of 2.19: Tricyclic **2.19** (mixture of two isomers 3:1) was prepared from **2.13a** in 71% yield by following the procedure for the preparation of **2.16**. The two isomers were then separated and identified by LC-MS (4.6 x 150 mm column, mobile phase A: hexane, mobile phase B: ethyl acetate; 0.00 min. 90:10, 30.00 min. 50:50, 30.01 min. 90:10).

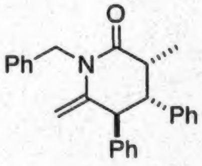
2.19 (major isomer): white solid; R$_f$ 0.22 (8:2 EtOAc//hexanes); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.60-3.50 (m, 1H), 3.50-3.40 (m, 2H), 2.30-1.90 (m, 5H), 1.90-1.60 (m, 6H), 1.50-1.30 (m, 2H), 1.24-1.10 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 172.1, 89.4, 81.6, 58.7, 44.6, 38.1, 35.3, 33.5, 31.0, 22.0, 20.7; HRMS (ESI) $[M+Na]^+$ for $C_{11}H_{17}NO_2Na$: calcd 218.1151, Found: *m/z* 218.1152.

Preparation of 2.20. To a solution of dibenzylidenepentanone[16] (100 mg, 0.038 mmol) and benzyl azide (100 mg, 0.76 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added $BF_3 \cdot OEt_2$ (0.058 mL, 0.46 mmol). After 30 min, the reaction mixture was stirred at 0 °C for 15 min; saturated aqueous $NaHCO_3$ (10 mL) was added and it was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were concentrated to give a mixture of two products **2.20a** and **2.20b**. The two products were then separated and purified by flash column chromatography (silica gel; 15:1 hexanes/EtOAc) to give 52 mg of **2.20a** and 50 mg of **2.20b** as colorless oils in yield 72%. **2.20a/2.20b**= 1:1 (determined by weighing each isomer after purification).



2.20a

2.20a: R_f 0.1 (15:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-6.90 (m, 15H), 5.13 (d, 1H, *J* = 15.6 Hz), 5.02 (d, 1H, *J* = 15.6 Hz), 4.50 (app t, 1H, *J* = 1.8 Hz), 3.90 (app dt, 1H, *J* = 11.8, 1.7 Hz), 3.77 (app t, 1H, *J* = 1.7 Hz), 3.05 (app t, 1H, *J* = 11.6 Hz), 2.85-2.93 (m, 1H), 1.14 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 148.2, 141.4, 141.0, 137.6, 129.3, 128.8, 128.5, 128.2, 128.1, 127.1, 126.9, 126.8, 126.7, 97.4, 53.2, 51.5, 48.2, 44.0, 15.8; HRMS (ESI) $[M+H]^+$ for $C_{26}H_{26}NO$: calcd 368.2008, Found: *m/z* 368.2008.



2.20b

2.20b: R_f 0.26 (15:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.05 (m, 15H), 5.15 (d, 1H, *J* = 15.2 Hz), 5.12 (d, 1H, *J* = 15.2 Hz), 4.62 (d, 1H, *J* = 1.5 Hz), 4.09-4.05 (m, 2H), 3.40 (app t, 1H, *J* = 5.2 Hz), 2.87 (app dq, 1H, *J* = 7.1, 5.5 Hz), 1.12 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.9, 143.3, 140.2, 137.6, 128.82, 128.80, 128.73, 128.72, 127.95, 127.91, 127.4, 127.1, 127.0, 97.6, 50.8, 49.9, 47.4, 37.0, 14.2; HRMS (ESI) $[M+H]^+$ for $C_{26}H_{26}NO$: calcd 368.2008, found: *m/z* 368.2004.

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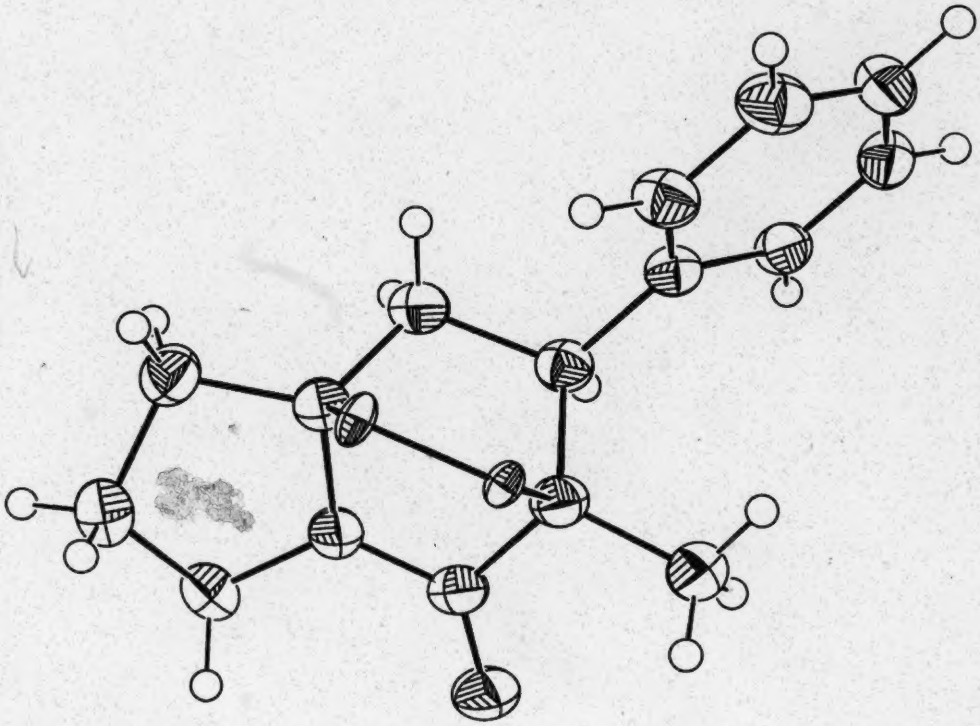
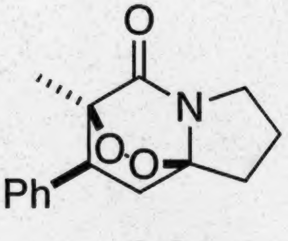
APPENDIX

A. X-RAY DIFRACTION DATA OF **2.8a** (CHAPTER 2)





2.8a

Table A.1 Crystal data and structure refinement for **2.8a**

Identification code	fgw001	
Empirical formula	C15 H17 N3 O	
Formula weight	255.32	
Temperature	200(1) K	
Wavelength	0.71069 Å	
Crystal system	Monoclinic	
Space group	P 21/a	
Unit cell dimensions	a = 12.7713(6) Å	a= 90°.
	b = 7.1779(2) Å	b= 105.7664(18)°.
	c = 14.2620(7) Å	g = 90.000(5)°.
Volume	1258.23(9) Å^3	
Z	4	
Density (calculated)	1.348 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	544	
Crystal size	0.21 x 0.16 x 0.13 mm^3	
Theta range for data collection	4.11 to 20.61°.	
Index ranges	0<=h<=12, 0<=k<=7, -14<=l<=13	
Reflections collected	1256	
Independent reflections	1256 [R(int) = 0.0000]	
Completeness to theta = 20.61°	98.0 %	
Absorption correction	Scalepack	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1256 / 0 / 173	
Goodness-of-fit on F^2	1.106	
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1127	
R indices (all data)	R1 = 0.0438, wR2 = 0.1150	
Extinction coefficient	0.046(8)	
Largest diff. peak and hole	0.284 and -0.183 e.Å^{-3}	

Table A.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.8a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7278(2)	6906(3)	3036(1)	44(1)
N(1)	7779(2)	3942(3)	3547(2)	33(1)
N(2)	6459(1)	2035(2)	3926(1)	19(1)
N(3)	5635(1)	3444(2)	3409(1)	16(1)
C(1)	8830(2)	4197(4)	4263(2)	36(1)
C(2)	8928(2)	2448(4)	4880(2)	42(1)
C(3)	8282(2)	983(4)	4192(2)	39(1)
C(4)	7371(2)	2051(3)	3505(2)	33(1)
C(5)	6965(2)	1428(4)	2455(2)	37(1)
C(6)	6117(2)	2847(4)	1881(2)	31(1)
C(7)	5967(2)	4333(3)	2617(2)	32(1)
C(8)	7075(2)	5246(4)	3079(2)	32(1)
C(9)	5085(2)	5744(4)	2237(2)	39(1)
C(10)	5068(2)	1982(3)	1292(2)	31(1)
C(11)	4479(2)	750(4)	1703(2)	37(1)
C(12)	3522(2)	-37(4)	1145(2)	42(1)
C(13)	3136(2)	380(4)	172(2)	41(1)
C(14)	3710(2)	1597(4)	-248(2)	39(1)
C(15)	4669(2)	2386(4)	308(2)	33(1)

Table A.3 Bond lengths [Å] and angles [°] for **2.8a**

O(1)-C(8)	1.225(3)
N(1)-C(8)	1.343(3)
N(1)-C(4)	1.449(3)
N(1)-C(1)	1.461(3)
N(2)-C(4)	1.448(3)
N(2)-N(3)	1.501(2)
N(3)-C(7)	1.457(3)
C(1)-C(2)	1.518(4)
C(2)-C(3)	1.519(4)
C(3)-C(4)	1.510(4)
C(4)-C(5)	1.513(4)
C(5)-C(6)	1.549(4)
C(6)-C(10)	1.508(4)
C(6)-C(7)	1.545(4)
C(7)-C(9)	1.502(4)
C(7)-C(8)	1.537(4)
C(10)-C(15)	1.387(4)
C(10)-C(11)	1.389(4)
C(11)-C(12)	1.385(4)
C(12)-C(13)	1.374(4)
C(13)-C(14)	1.377(4)
C(14)-C(15)	1.387(4)
C(8)-N(1)-C(4)	116.6(2)
C(8)-N(1)-C(1)	128.6(2)
C(4)-N(1)-C(1)	113.4(2)
C(4)-N(2)-N(3)	109.05(16)
C(7)-N(3)-N(2)	111.31(16)
N(1)-C(1)-C(2)	102.5(2)
C(1)-C(2)-C(3)	104.7(2)
C(4)-C(3)-C(2)	104.8(2)
N(2)-C(4)-N(1)	108.2(2)

N(2)-C(4)-C(3)	106.9(2)
N(1)-C(4)-C(3)	104.1(2)
N(2)-C(4)-C(5)	108.1(2)
N(1)-C(4)-C(5)	109.9(2)
C(3)-C(4)-C(5)	119.2(2)
C(4)-C(5)-C(6)	109.3(2)
C(10)-C(6)-C(7)	114.0(2)
C(10)-C(6)-C(5)	114.3(2)
C(7)-C(6)-C(5)	107.0(2)
N(3)-C(7)-C(9)	103.2(2)
N(3)-C(7)-C(8)	106.41(19)
C(9)-C(7)-C(8)	112.4(2)
N(3)-C(7)-C(6)	109.9(2)
C(9)-C(7)-C(6)	116.0(2)
C(8)-C(7)-C(6)	108.4(2)
O(1)-C(8)-N(1)	125.5(2)
O(1)-C(8)-C(7)	125.2(2)
N(1)-C(8)-C(7)	109.3(2)
C(15)-C(10)-C(11)	117.9(2)
C(15)-C(10)-C(6)	120.3(2)
C(11)-C(10)-C(6)	121.9(2)
C(12)-C(11)-C(10)	120.8(2)
C(13)-C(12)-C(11)	120.6(3)
C(12)-C(13)-C(14)	119.4(3)
C(13)-C(14)-C(15)	120.1(3)
C(14)-C(15)-C(10)	121.2(2)

Symmetry transformations used to generate equivalent atoms:

Table A.4 Anisotropic displacement parameters ($Å^2$x 10^3) for **2.8a**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	54(1)	27(1)	49(1)	-1(1)	10(1)	-6(1)
N(1)	35(1)	27(1)	34(1)	0(1)	5(1)	-3(1)
N(2)	20(1)	18(1)	21(1)	12(1)	8(1)	4(1)
N(3)	18(1)	16(1)	15(1)	5(1)	7(1)	4(1)
C(1)	33(2)	40(2)	33(2)	-5(1)	7(1)	-5(1)
C(2)	38(2)	47(2)	37(2)	2(1)	5(1)	2(1)
C(3)	41(2)	34(2)	41(2)	5(1)	9(1)	2(1)
C(4)	35(2)	27(2)	35(2)	1(1)	6(1)	-2(1)
C(5)	38(2)	31(2)	40(2)	-5(1)	8(1)	0(1)
C(6)	35(2)	29(2)	31(2)	1(1)	10(1)	-3(1)
C(7)	38(2)	26(2)	32(2)	-1(1)	9(1)	0(1)
C(8)	43(2)	25(2)	29(2)	-1(1)	13(1)	-1(2)
C(9)	43(2)	34(2)	37(2)	0(1)	7(1)	3(1)
C(10)	33(2)	28(2)	31(2)	-3(1)	9(1)	1(1)
C(11)	42(2)	36(2)	33(2)	-3(1)	11(1)	-4(1)
C(12)	41(2)	39(2)	50(2)	-7(1)	19(2)	-7(1)
C(13)	32(2)	41(2)	47(2)	-9(2)	3(1)	-2(1)
C(14)	42(2)	37(2)	34(2)	-2(1)	4(2)	7(2)
C(15)	38(2)	28(2)	34(2)	-1(1)	10(1)	1(1)

Table A.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2.8a**.

	x	y	z	U(eq)
H(1A)	8833	5308	4651	43
H(1B)	9415	4277	3951	43
H(2A)	8625	2647	5426	50
H(2B)	9683	2075	5126	50
H(3A)	8734	369	3838	47
H(3B)	7994	52	4548	47
H(5A)	6635	205	2425	44
H(5B)	7570	1346	2167	44
H(6)	6444	3476	1420	38
H(9A)	4410	5113	1953	59
H(9B)	5272	6500	1751	59
H(9C)	5010	6520	2763	59
H(11)	4731	449	2360	44
H(12)	3136	-856	1432	50
H(13)	2494	-154	-200	49
H(14)	3453	1891	-906	47
H(15)	5052	3201	16	40

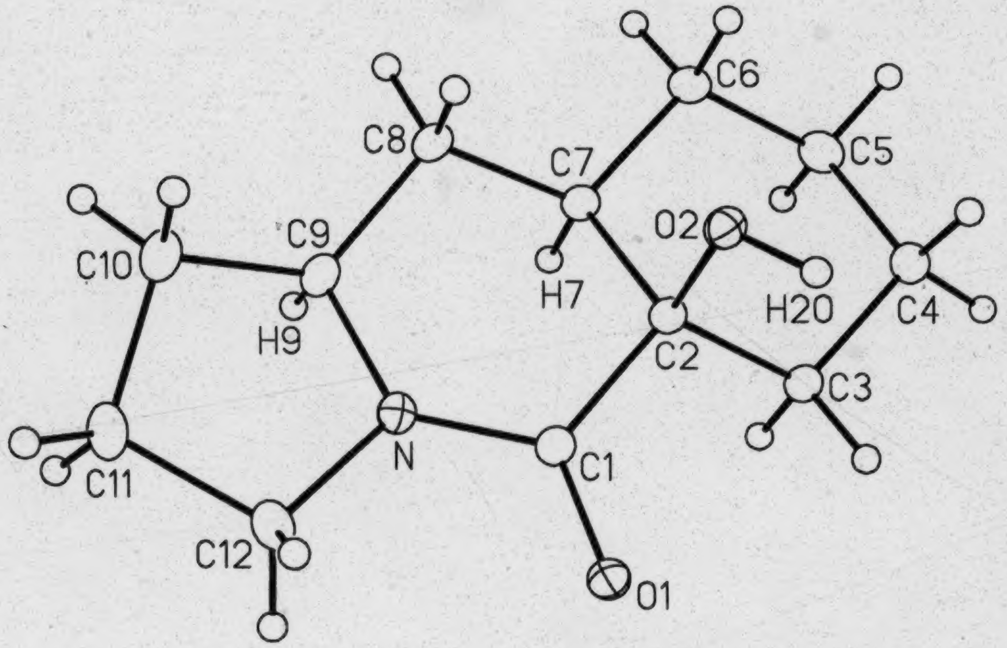
Table A.6 Torsion angles [°] for **2.8a.**

C(4)-N(2)-N(3)-C(7)	2.8(2)
C(8)-N(1)-C(1)-C(2)	151.0(2)
C(4)-N(1)-C(1)-C(2)	-15.1(3)
N(1)-C(1)-C(2)-C(3)	28.8(3)
C(1)-C(2)-C(3)-C(4)	-32.6(3)
N(3)-N(2)-C(4)-N(1)	54.9(2)
N(3)-N(2)-C(4)-C(3)	166.50(18)
N(3)-N(2)-C(4)-C(5)	-64.0(2)
C(8)-N(1)-C(4)-N(2)	-59.4(3)
C(1)-N(1)-C(4)-N(2)	108.5(2)
C(8)-N(1)-C(4)-C(3)	-172.8(2)
C(1)-N(1)-C(4)-C(3)	-5.0(3)
C(8)-N(1)-C(4)-C(5)	58.4(3)
C(1)-N(1)-C(4)-C(5)	-133.8(2)
C(2)-C(3)-C(4)-N(2)	-91.3(2)
C(2)-C(3)-C(4)-N(1)	23.1(3)
C(2)-C(3)-C(4)-C(5)	145.9(2)
N(2)-C(4)-C(5)-C(6)	63.3(3)
N(1)-C(4)-C(5)-C(6)	-54.5(3)
C(3)-C(4)-C(5)-C(6)	-174.5(2)
C(4)-C(5)-C(6)-C(10)	-129.8(2)
C(4)-C(5)-C(6)-C(7)	-2.5(3)
N(2)-N(3)-C(7)-C(9)	-176.94(17)
N(2)-N(3)-C(7)-C(8)	-58.5(2)
N(2)-N(3)-C(7)-C(6)	58.7(2)
C(10)-C(6)-C(7)-N(3)	70.4(3)
C(5)-C(6)-C(7)-N(3)	-57.0(2)
C(10)-C(6)-C(7)-C(9)	-46.2(3)
C(5)-C(6)-C(7)-C(9)	-173.6(2)
C(10)-C(6)-C(7)-C(8)	-173.7(2)
C(5)-C(6)-C(7)-C(8)	58.9(3)
C(4)-N(1)-C(8)-O(1)	-179.9(2)

C(1)-N(1)-C(8)-O(1)	14.4(4)
C(4)-N(1)-C(8)-C(7)	0.9(3)
C(1)-N(1)-C(8)-C(7)	-164.8(2)
N(3)-C(7)-C(8)-O(1)	-121.7(3)
C(9)-C(7)-C(8)-O(1)	-9.5(4)
C(6)-C(7)-C(8)-O(1)	120.1(3)
N(3)-C(7)-C(8)-N(1)	57.4(2)
C(9)-C(7)-C(8)-N(1)	169.7(2)
C(6)-C(7)-C(8)-N(1)	-60.8(3)
C(7)-C(6)-C(10)-C(15)	109.2(3)
C(5)-C(6)-C(10)-C(15)	-127.3(3)
C(7)-C(6)-C(10)-C(11)	-71.7(3)
C(5)-C(6)-C(10)-C(11)	51.9(3)
C(15)-C(10)-C(11)-C(12)	-0.4(4)
C(6)-C(10)-C(11)-C(12)	-179.5(2)
C(10)-C(11)-C(12)-C(13)	0.2(4)
C(11)-C(12)-C(13)-C(14)	-0.2(4)
C(12)-C(13)-C(14)-C(15)	0.2(4)
C(13)-C(14)-C(15)-C(10)	-0.4(4)
C(11)-C(10)-C(15)-C(14)	0.4(4)
C(6)-C(10)-C(15)-C(14)	179.6(2)

Symmetry transformations used to generate equivalent atoms:

B. X-RAY DIFRACTION DATA OF **2.16** (CHAPTER 2)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C5
C7
O2
C9
C10
H7
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C4
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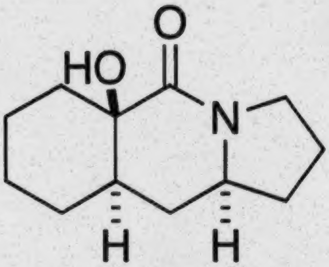
C2
C3
N
C11
C1
C12
O1



2.16

Table B.1 Crystallographic Experimental Details for **2.16**

A. Crystal Data	
formula	$C_{12}H_{19}NO_2$
formula weight	209.28
crystal dimensions (mm)	0.41 × 0.26 × 0.20
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	8.8461 (6)
b (Å)	12.6516 (9)
c (Å)	9.8467 (7)
β (deg)	95.9990 (10)
V (Å^3)	1095.98 (13)
Z	4
ρ_{calcd} (g cm^{-3})	1.268
μ (mm^{-1})	0.086
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	52.78
total data collected	8219 ($-11 \leq h \leq 11$, $-15 \leq k \leq 15$, $-12 \leq l \leq 12$)
independent reflections	2243 ($R_{\mathrm{int}} = 0.0227$)
number of observed reflections (*NO*)	1959 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9831–0.9658
data/restraints/parameters	2243 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 137
goodness-of-fit (*S*)[e]	1.049 [$F_o^2 \geq -3\sigma(F_o^2)$]
final *R* indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0398
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.1101
largest difference peak and hole	0.294 and –0.206 e Å^{-3}

[a] Obtained from least-squares refinement of 5507 reflections with $4.64° < 2\theta < 52.76°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

Table B.1. Crystallographic Experimental Details for **2.16** (continued)

[c] Sheldrick, G. M. *Acta Crystallogr.* **1990,** *A46*, 467–473.

[d] Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[e] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0592P)^2 + 0.2806P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table B.2 Atomic Coordinates and Equivalent Isotropic Displacement Parameters for **2.16**

Atom	x	y	z	U_{eq}, Å^2
O1	0.37726(10)	-0.01330(7)	0.32337(9)	0.0328(2)*
O2	0.36190(9)	0.11546(7)	0.58082(8)	0.0280(2)*
N	0.15502(11)	0.07229(8)	0.30776(10)	0.0298(3)*
C1	0.30334(13)	0.06537(9)	0.35111(11)	0.0249(3)*
C2	0.37328(12)	0.15357(9)	0.44484(11)	0.0239(3)*
C3	0.53822(13)	0.17435(10)	0.41999(12)	0.0272(3)*
C4	0.61071(14)	0.25799(10)	0.51792(13)	0.0329(3)*
C5	0.51787(16)	0.36009(10)	0.50987(14)	0.0366(3)*
C6	0.35170(14)	0.33919(10)	0.52935(13)	0.0322(3)*
C7	0.28154(13)	0.25673(9)	0.42867(12)	0.0266(3)*
C8	0.11468(14)	0.23249(11)	0.44064(13)	0.0321(3)*
C9	0.05429(13)	0.16335(11)	0.32268(14)	0.0340(3)*
C10	-0.09845(15)	0.11049(13)	0.32451(16)	0.0456(4)*
C11	-0.09347(16)	0.02107(14)	0.22123(16)	0.0473(4)*
C12	0.07227(15)	-0.01628(12)	0.23834(14)	0.0379(3)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table B.3 Selected Interatomic Distances (Å) for **2.16**

Atom1	Atom2	Distance
O1	O2’	2.7257(11)†
O1	C1	1.2370(14)
O1	H2O’	1.89†
O2	C2	1.4365(13)
N	C1	1.3395(15)
N	C9	1.4732(16)
N	C12	1.4677(16)
C1	C2	1.5364(16)
C2	C3	1.5273(15)
C2	C7	1.5363(15)
C3	C4	1.5270(16)
C4	C5	1.5283(18)
C5	C6	1.5253(18)
C6	C7	1.5256(16)
C7	C8	1.5242(17)
C8	C9	1.5066(18)
C9	C10	1.5094(18)
C10	C11	1.525(2)
C11	C12	1.5328(19)

Table B.4 Selected Interatomic Angles (deg) for **2.16**

Atom1	Atom2	Atom3	Angle
C1	N	C9	127.01(10)
C1	N	C12	121.51(10)
C9	N	C12	111.47(10)
O1	C1	N	120.34(11)
O1	C1	C2	121.88(10)
N	C1	C2	117.61(10)
O2	C2	C1	104.66(9)
O2	C2	C3	111.61(9)
O2	C2	C7	107.10(9)
C1	C2	C3	111.11(9)
C1	C2	C7	112.31(9)

C3	C2	C7	109.90(10)
C2	C3	C4	111.30(10)
C3	C4	C5	111.41(10)
C4	C5	C6	111.51(11)
C5	C6	C7	111.64(10)
C2	C7	C6	109.81(9)
C2	C7	C8	109.05(10)
C6	C7	C8	114.76(10)
C7	C8	C9	108.99(10)
N	C9	C8	111.19(10)
N	C9	C10	101.90(11)
C8	C9	C10	119.59(11)
C9	C10	C11	103.44(11)
C10	C11	C12	104.44(11)
N	C12	C11	103.92(11)
O1	H2O'	O2'	173.3‡

Primed atoms are related to unprimed ones via the crystallographic inversion center ($^{1}/2$, 0, $^{1}/2$). †Angle includes nonbonded O···H–O interaction.

Table B.5 Torsional Angles (deg) for **2.16**

Atom1	Atom2	Atom3	Atom4	Angle
C9	N	C1	O1	-174.87(11)
C9	N	C1	C2	9.92(17)
C12	N	C1	O1	6.04(17)
C12	N	C1	C2	-169.17(10)
C1	N	C9	C8	-23.69(17)
C1	N	C9	C10	-152.22(12)
C12	N	C9	C8	155.47(11)
C12	N	C9	C10	26.95(14)
C1	N	C12	C11	174.18(11)
C9	N	C12	C11	-5.04(15)
O1	C1	C2	O2	-82.46(12)
O1	C1	C2	C3	38.14(14)
O1	C1	C2	C7	161.70(10)
N	C1	C2	O2	92.67(11)

N	C1	C2	C3	-146.73(10)
N	C1	C2	C7	-23.17(14)
O2	C2	C3	C4	-60.69(13)
C1	C2	C3	C4	-177.10(9)
C7	C2	C3	C4	57.98(12)
O2	C2	C7	C6	62.70(12)
O2	C2	C7	C8	-63.84(11)
C1	C2	C7	C6	177.06(9)
C1	C2	C7	C8	50.52(12)
C3	C2	C7	C6	-58.71(12)
C3	C2	C7	C8	174.75(9)
C2	C3	C4	C5	-55.12(14)
C3	C4	C5	C6	53.01(14)
C4	C5	C6	C7	-54.72(14)
C5	C6	C7	C2	57.47(13)
C5	C6	C7	C8	-179.28(10)
C2	C7	C8	C9	-64.94(12)
C6	C7	C8	C9	171.41(10)
C7	C8	C9	N	49.83(14)
C7	C8	C9	C10	168.15(12)
N	C9	C10	C11	-37.55(14)
C8	C9	C10	C11	-160.53(12)
C9	C10	C11	C12	35.47(16)
C10	C11	C12	N	-18.91(15)

Table B.6 Anisotropic Displacement Parameters (U_{ij}, Å^2) for **2.16**

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}
O1	0.0335(5)	0.0273(5)	0.0362(5)	-0.0044(4)	-0.0028(4)
O2	0.0276(4)	0.0318(5)	0.0248(4)	0.0044(3)	0.0037(3)
N	0.0243(5)	0.0316(6)	0.0333(5)	-0.0034(4)	0.0025(4)
C1	0.0260(6)	0.0255(6)	0.0235(5)	0.0032(4)	0.0038(4)
C2	0.0235(5)	0.0255(6)	0.0227(5)	0.0014(4)	0.0032(4)
C3	0.0244(6)	0.0290(6)	0.0285(6)	-0.0009(5)	0.0048(4)
C4	0.0282(6)	0.0336(7)	0.0368(7)	-0.0039(5)	0.0027(5)
C5	0.0430(7)	0.0269(6)	0.0395(7)	-0.0030(5)	0.0023(6)
C6	0.0378(7)	0.0255(6)	0.0329(6)	-0.0031(5)	0.0014(5)
C7	0.0283(6)	0.0257(6)	0.0257(6)	0.0006(4)	0.0020(4)
C8	0.0277(6)	0.0355(7)	0.0332(6)	-0.0014(5)	0.0038(5)
C9	0.0246(6)	0.0411(7)	0.0361(7)	-0.0006(6)	0.0030(5)

C10	0.0258(7)	0.0650(10)	0.0460(8)	-0.0050(7)	0.0035(6)
C11	0.0306(7)	0.0625(10)	0.0480(8)	-0.0069(7)	-0.0003(6)
C12	0.0328(7)	0.0409(8)	0.0393(7)	-0.0061(6)	0.0001(5)

U_{12}
0.0071(4)
0.0050(3)
0.0009(4)
0.0015(4)
0.0024(4)
0.0000(4)
0.0039(5)
0.0048(5)
0.0069(5)
0.0055(5)
0.0094(5)
0.0057(5)
0.0004(6)
0.0094(7)
0.0081(6)

The form of the anisotropic displacement parameter is:

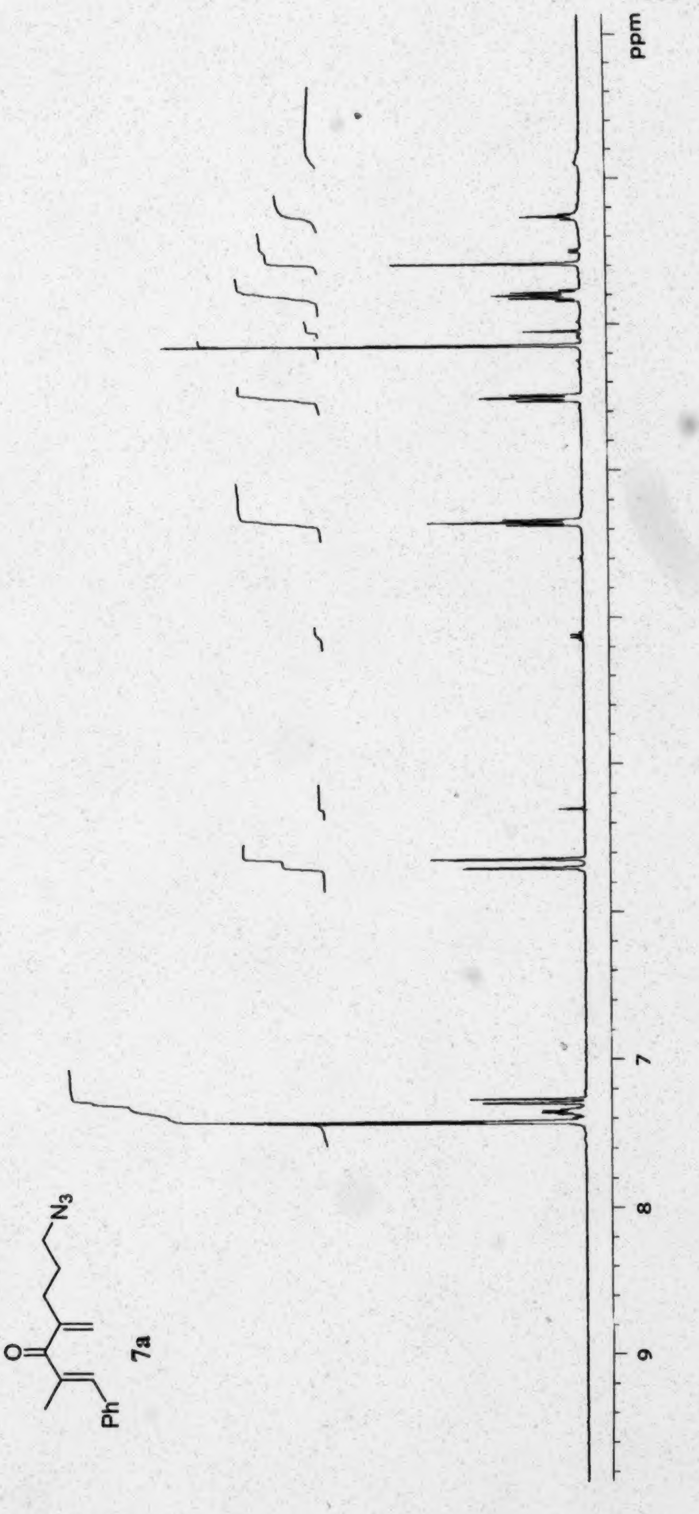
$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table B.7 Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms for **2.16**

Atom	x	y	z	U_{eq}, Å^2
H2O	0.4394	0.0796	0.6070	0.042
H3A	0.5969	0.1078	0.4323	0.033
H3B	0.5419	0.1984	0.3247	0.033
H4A	0.7149	0.2732	0.4951	0.040
H4B	0.6183	0.2303	0.6124	0.040
H5A	0.5616	0.4097	0.5812	0.044
H5B	0.5240	0.3938	0.4199	0.044
H6A	0.2936	0.4060	0.5166	0.039
H6B	0.3445	0.3142	0.6238	0.039
H7	0.2894	0.2841	0.3344	0.032
H8A	0.1043	0.1958	0.5280	0.039
H8B	0.0558	0.2991	0.4393	0.039
H9	0.0513	0.2065	0.2374	0.041
H10A	-0.1822	0.1603	0.2965	0.055

H10B	-0.1115	0.0826	0.4165	0.055
H11A	-0.1225	0.0469	0.1272	0.057
H11B	-0.1629	-0.0369	0.2411	0.057
H12A	0.0837	-0.0813	0.2944	0.046
H12B	0.1092	-0.0303	0.1486	

C. SELECTED ^{1}H AND ^{13}C SPECTRA



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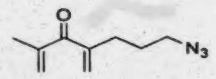

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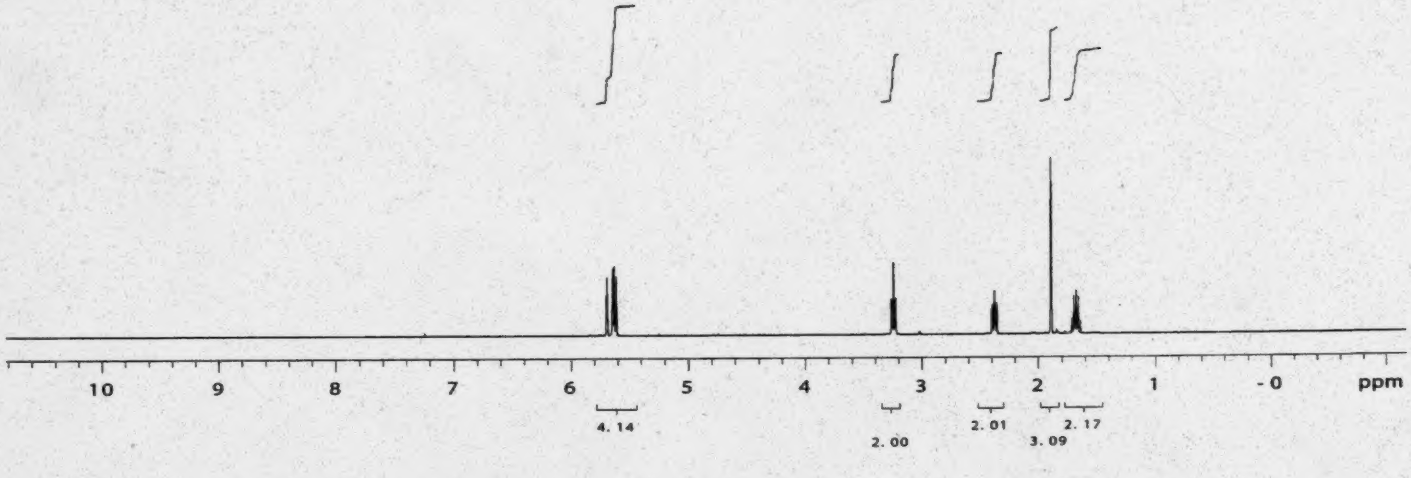

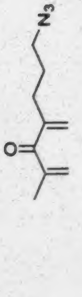

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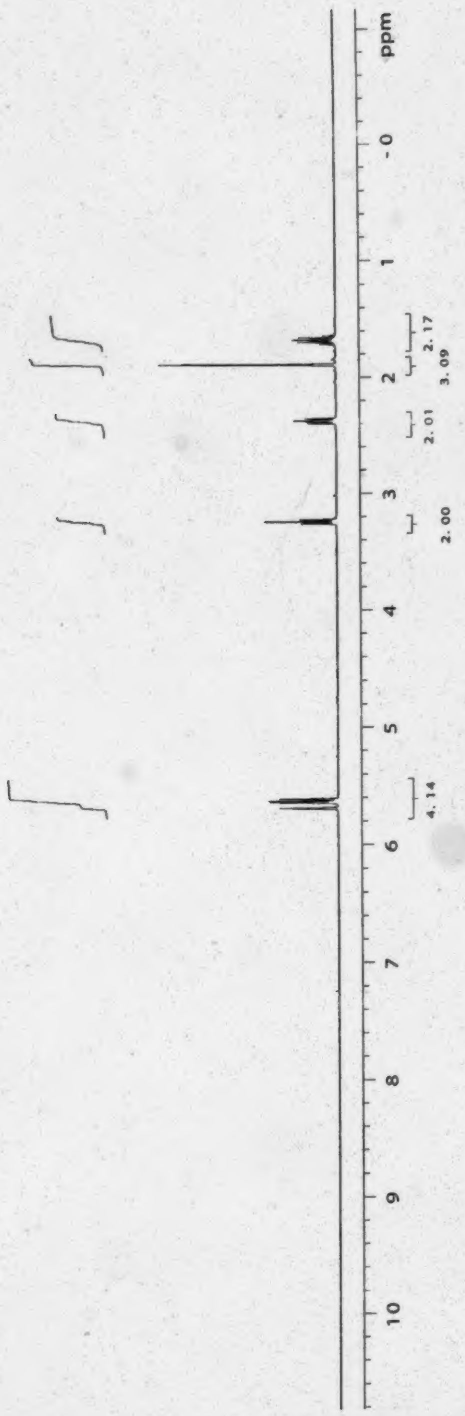

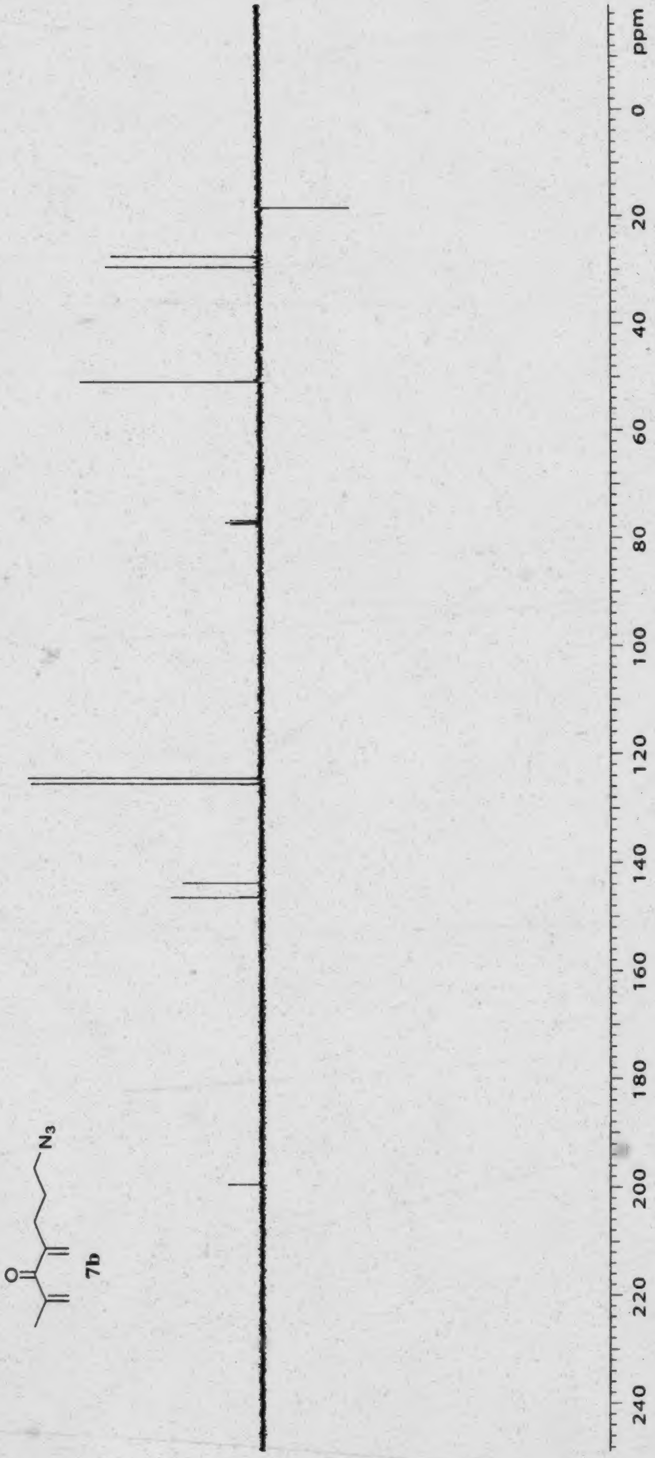

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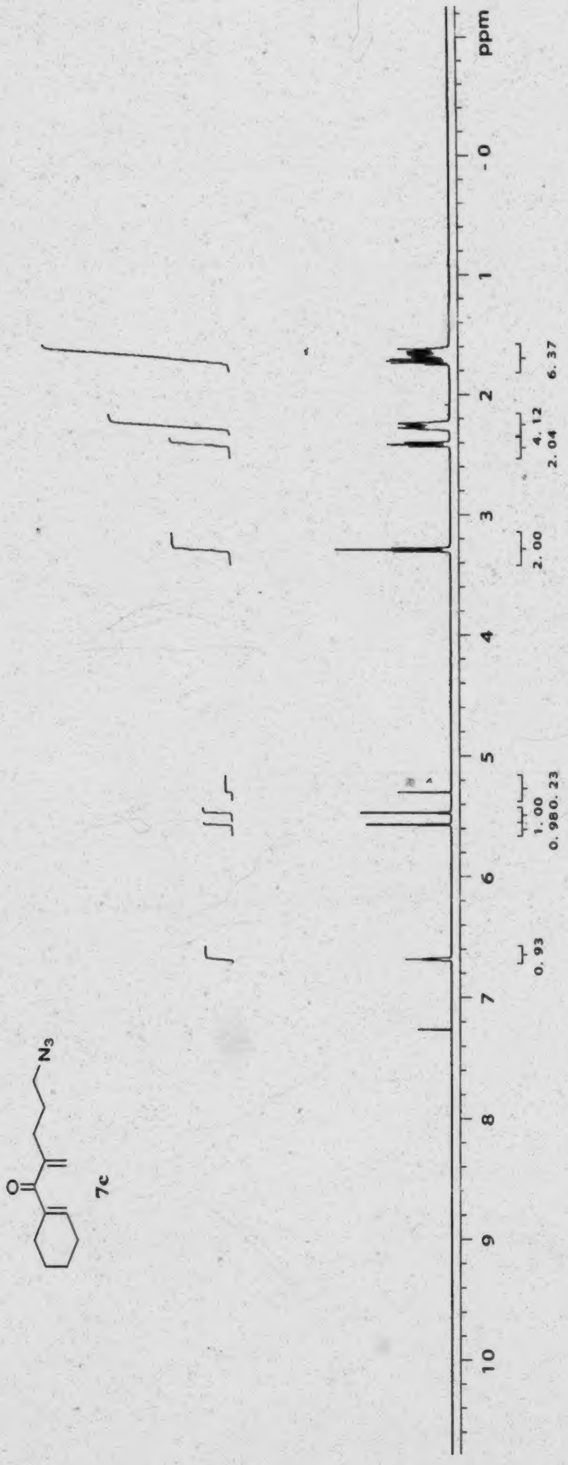

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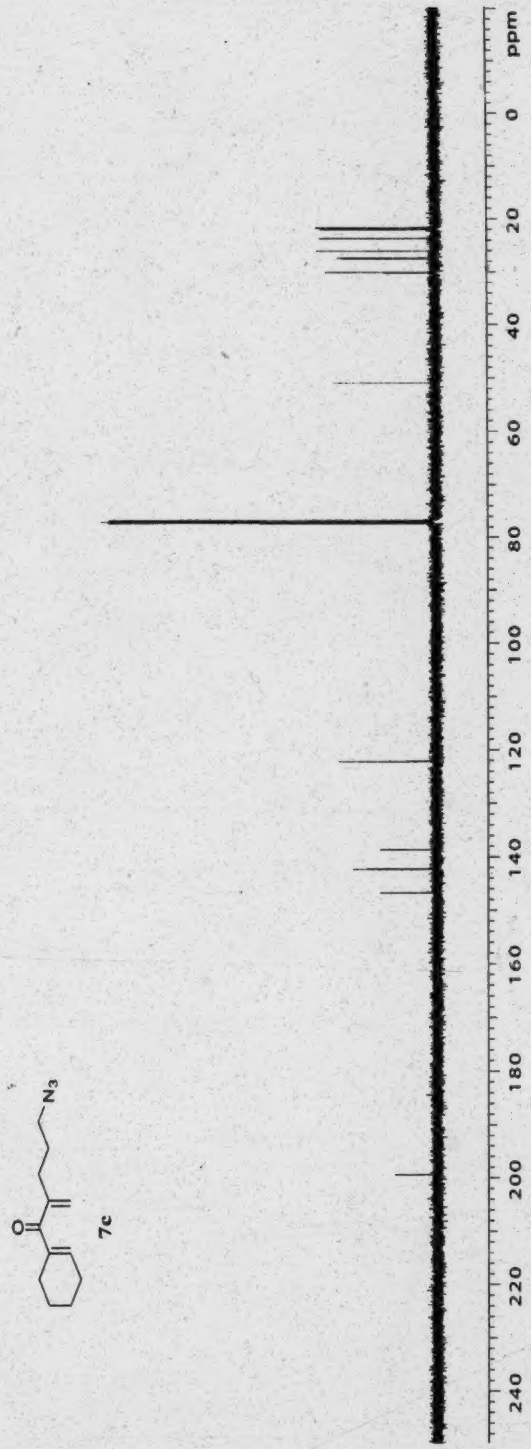

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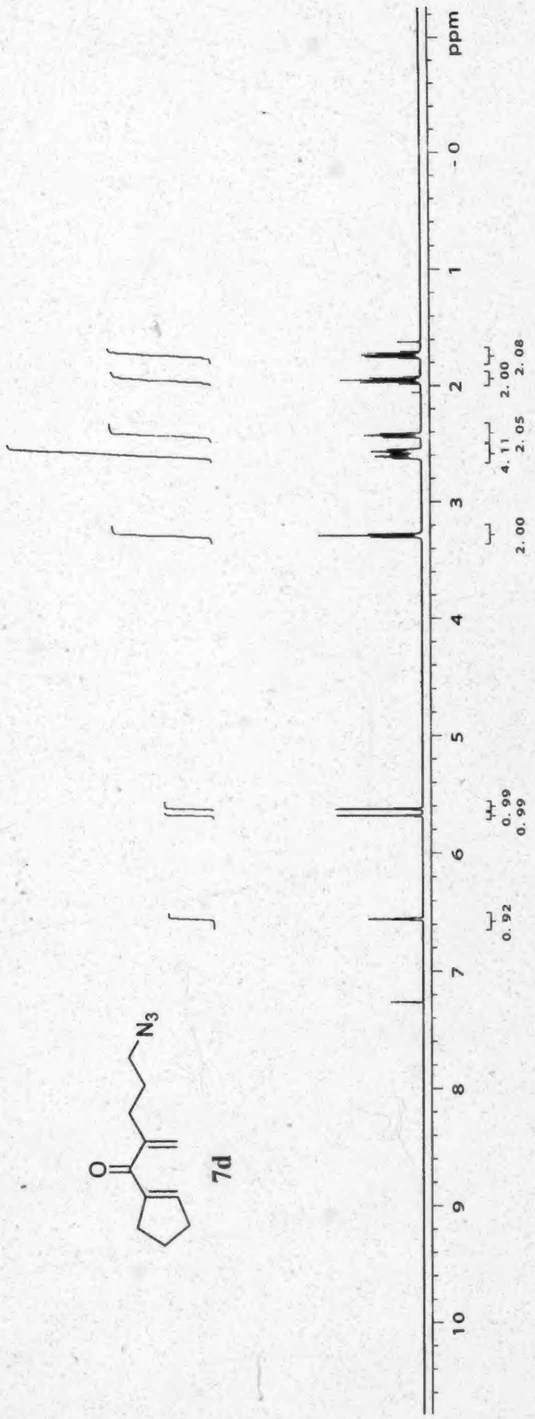

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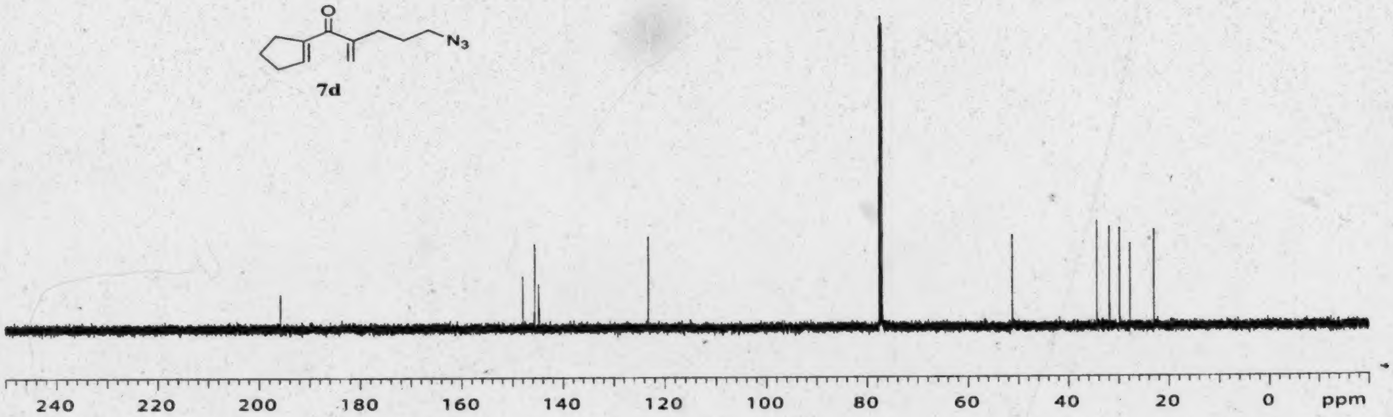

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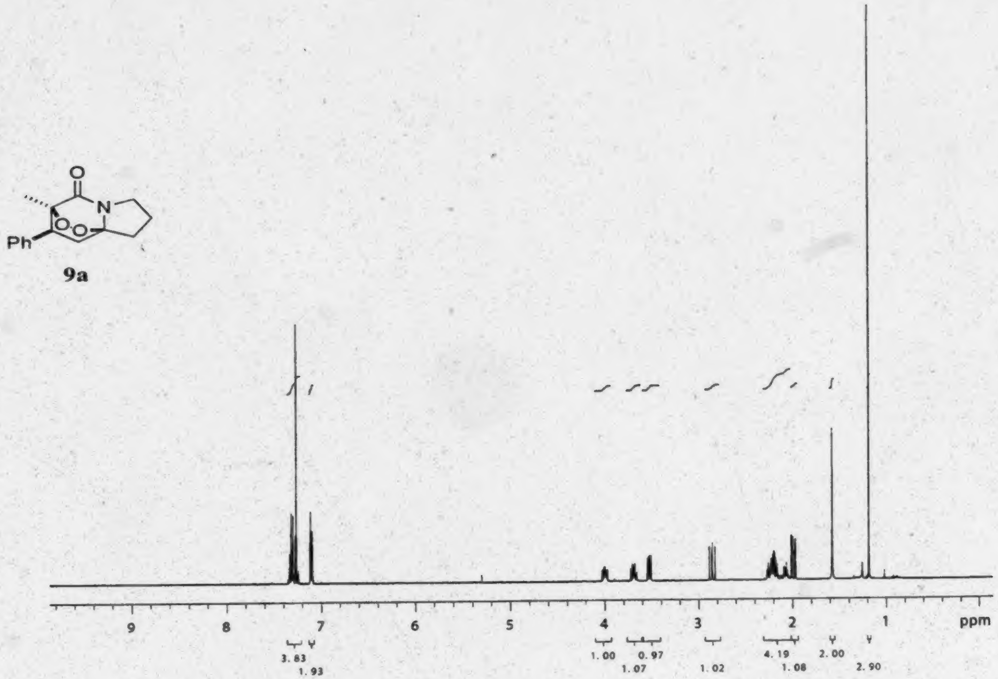

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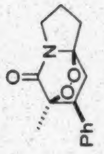

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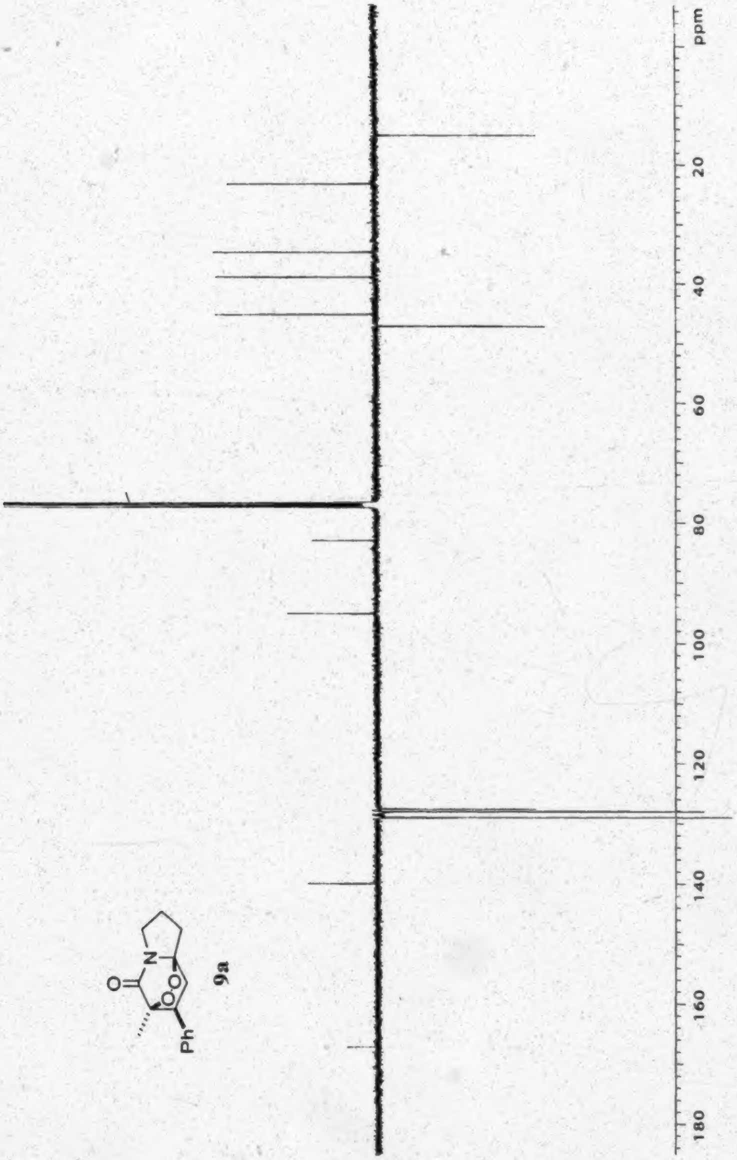

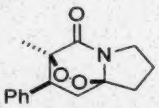

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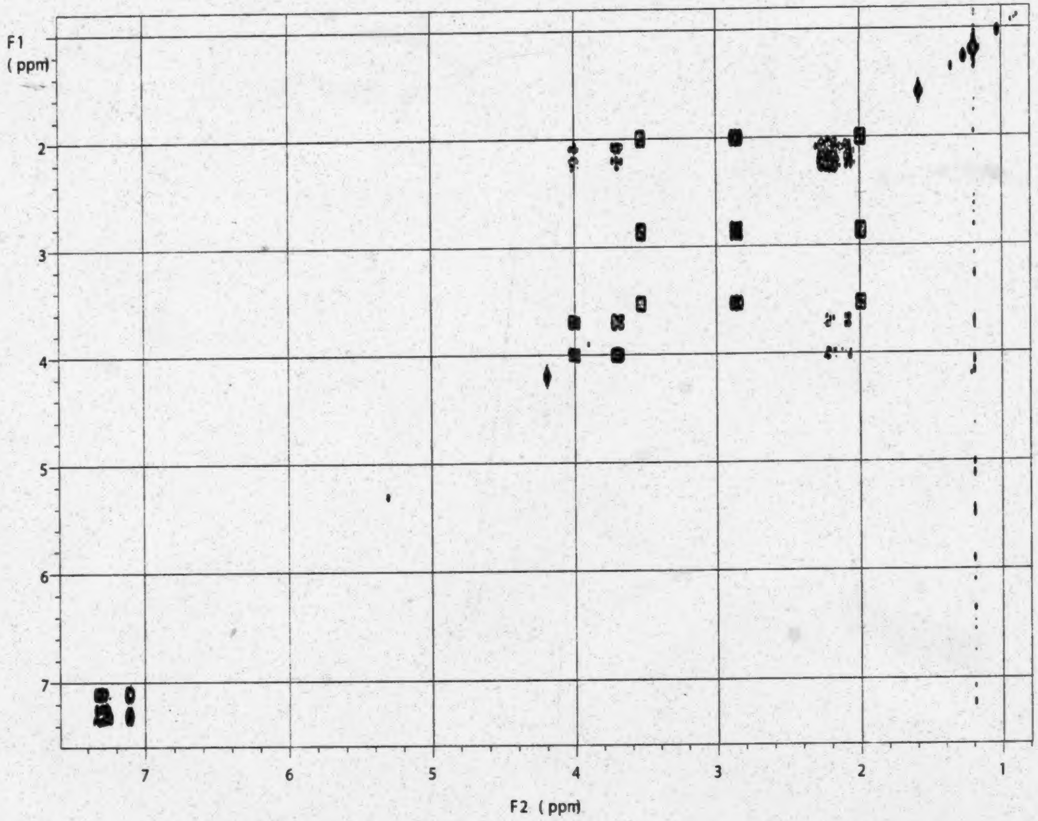

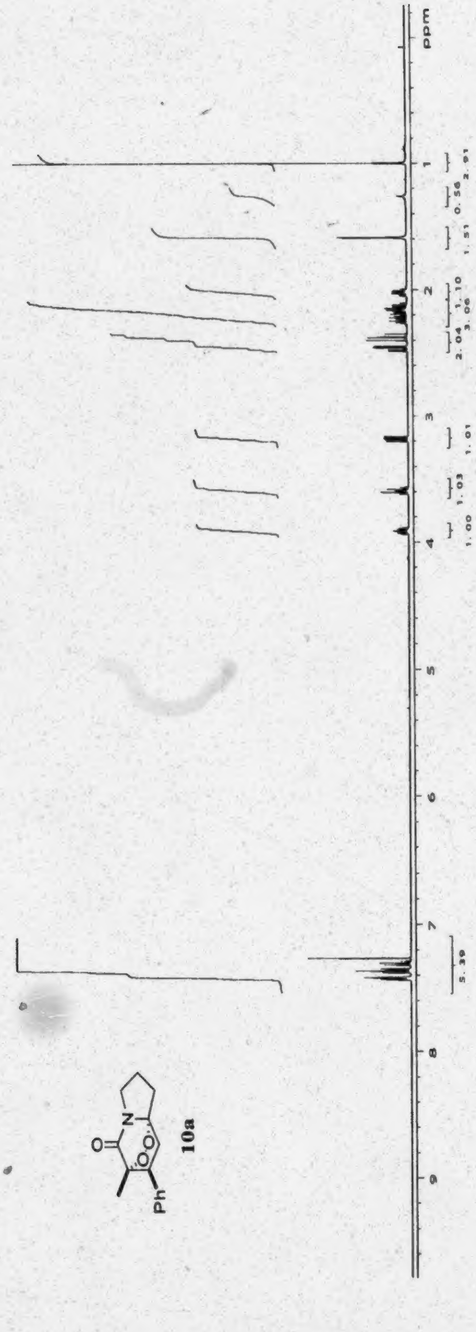

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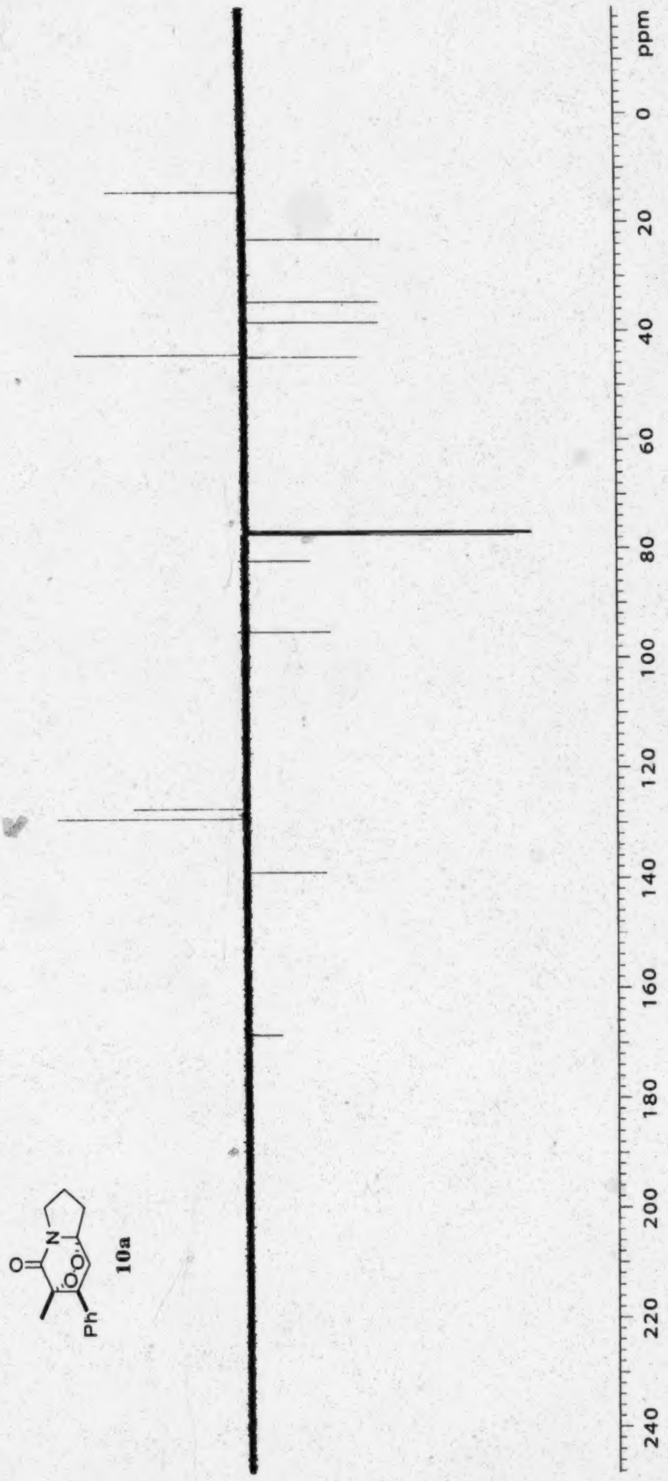

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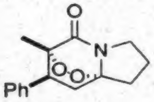

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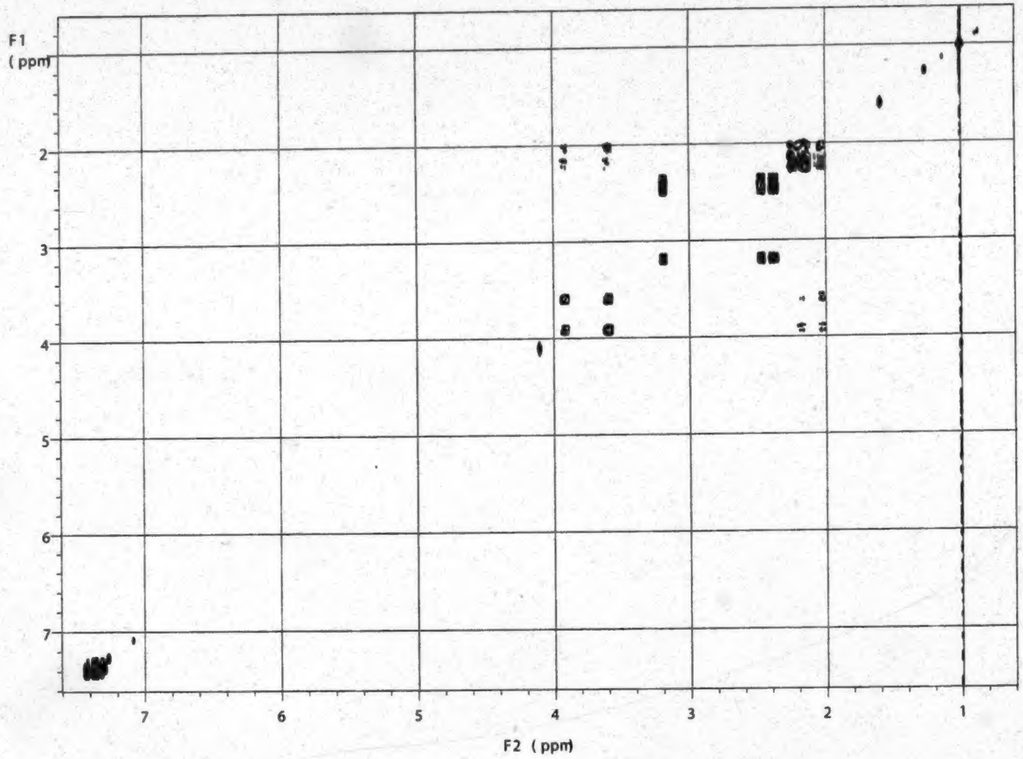

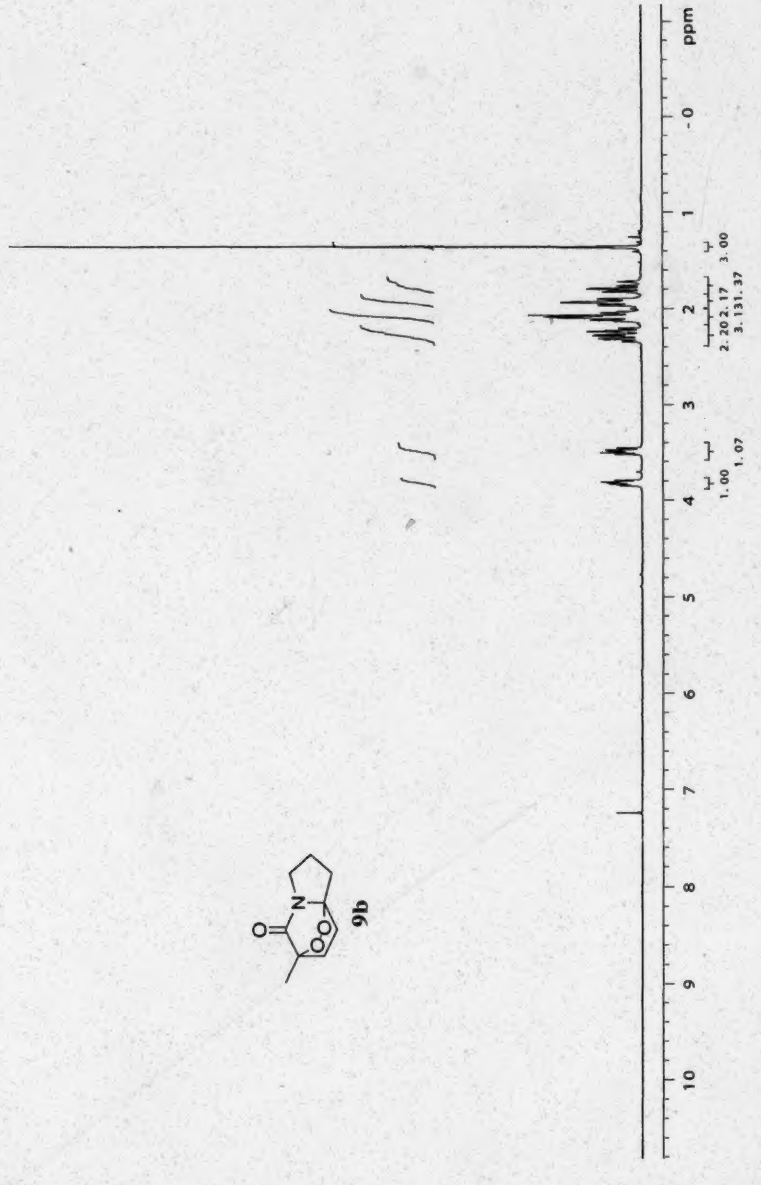
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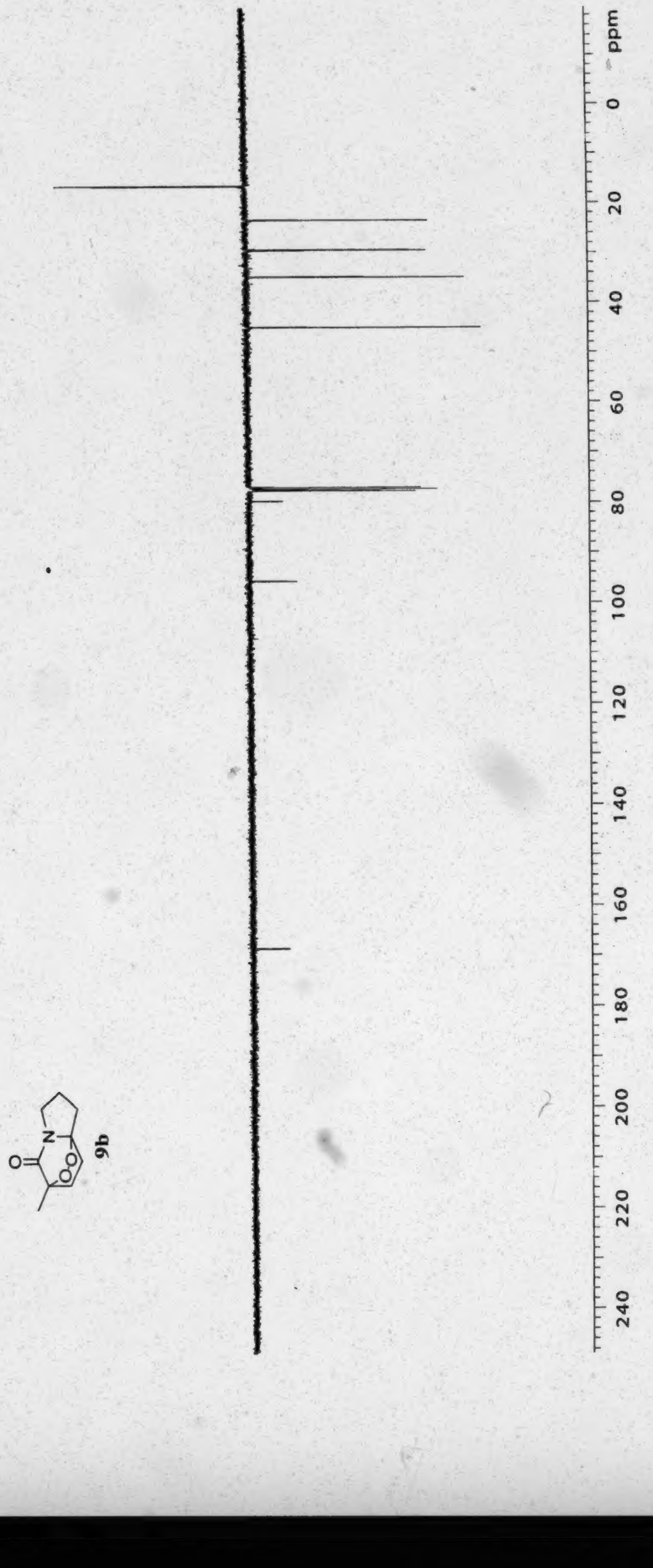

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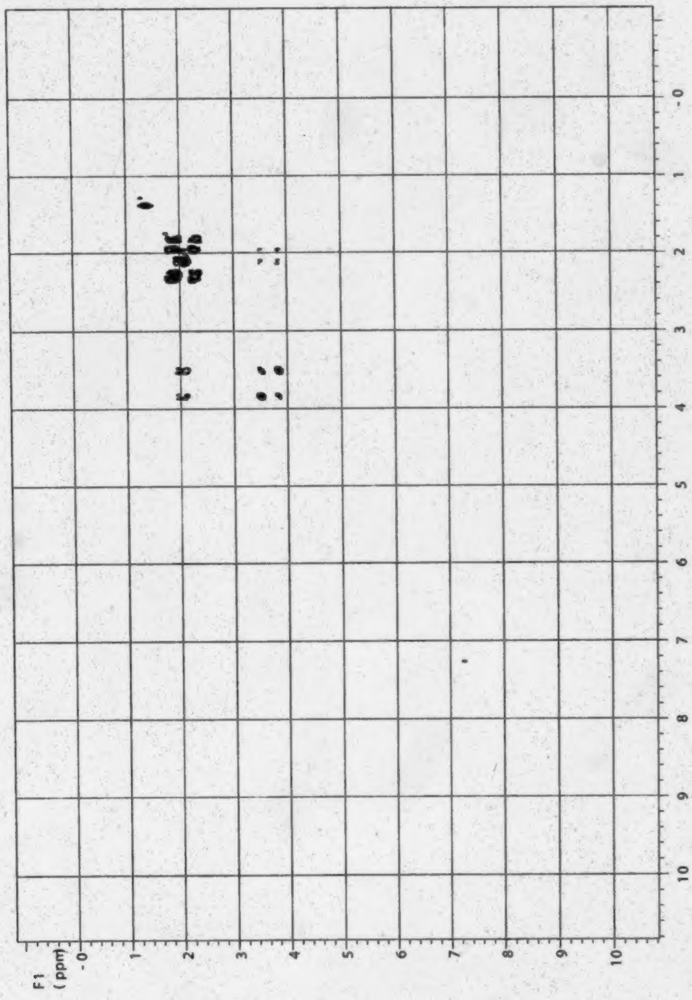

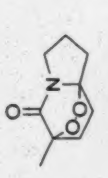

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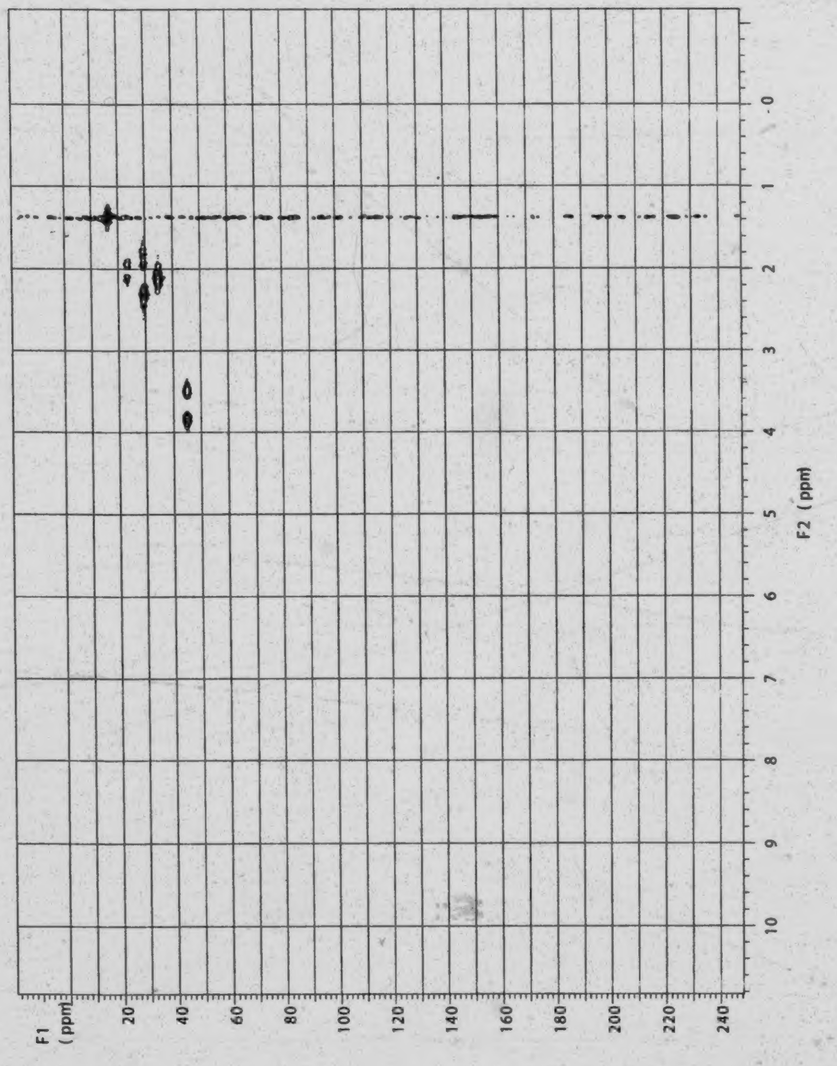
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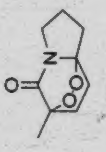
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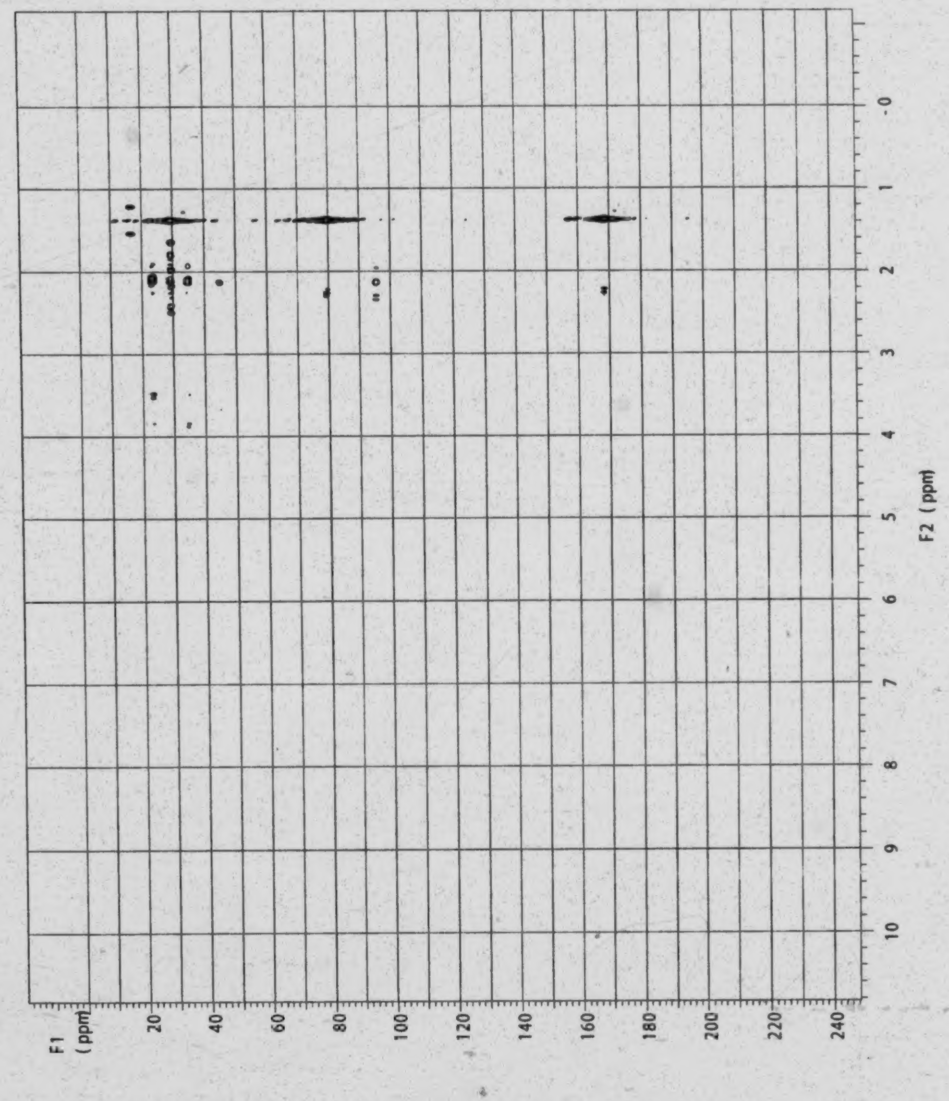
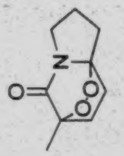
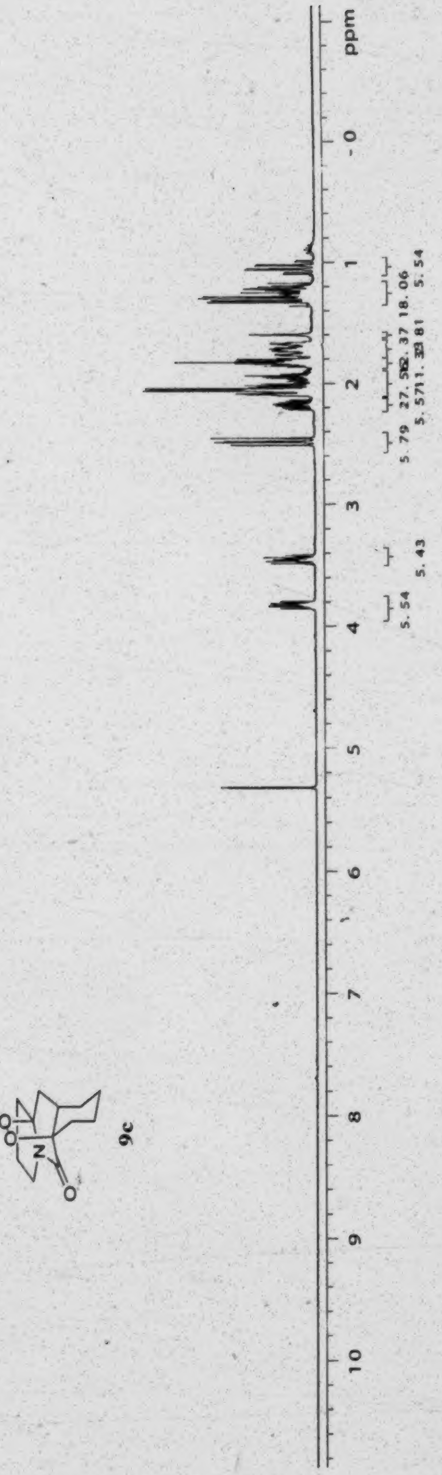
9b
HMQC

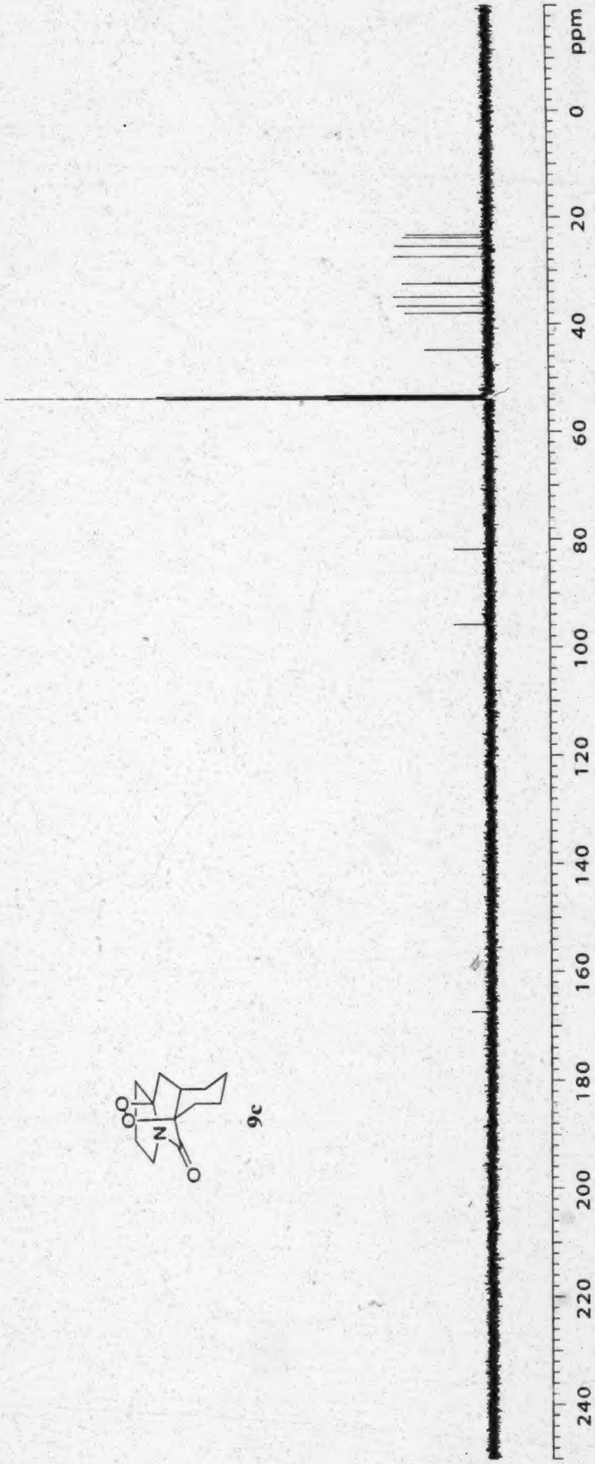

F1 (ppm)
20
40
60
80
100
120
140
160
180
200
220
240
F2 (ppm)
-0
1
2
3
4
5
6
7
8
9
10


O
N
O
O

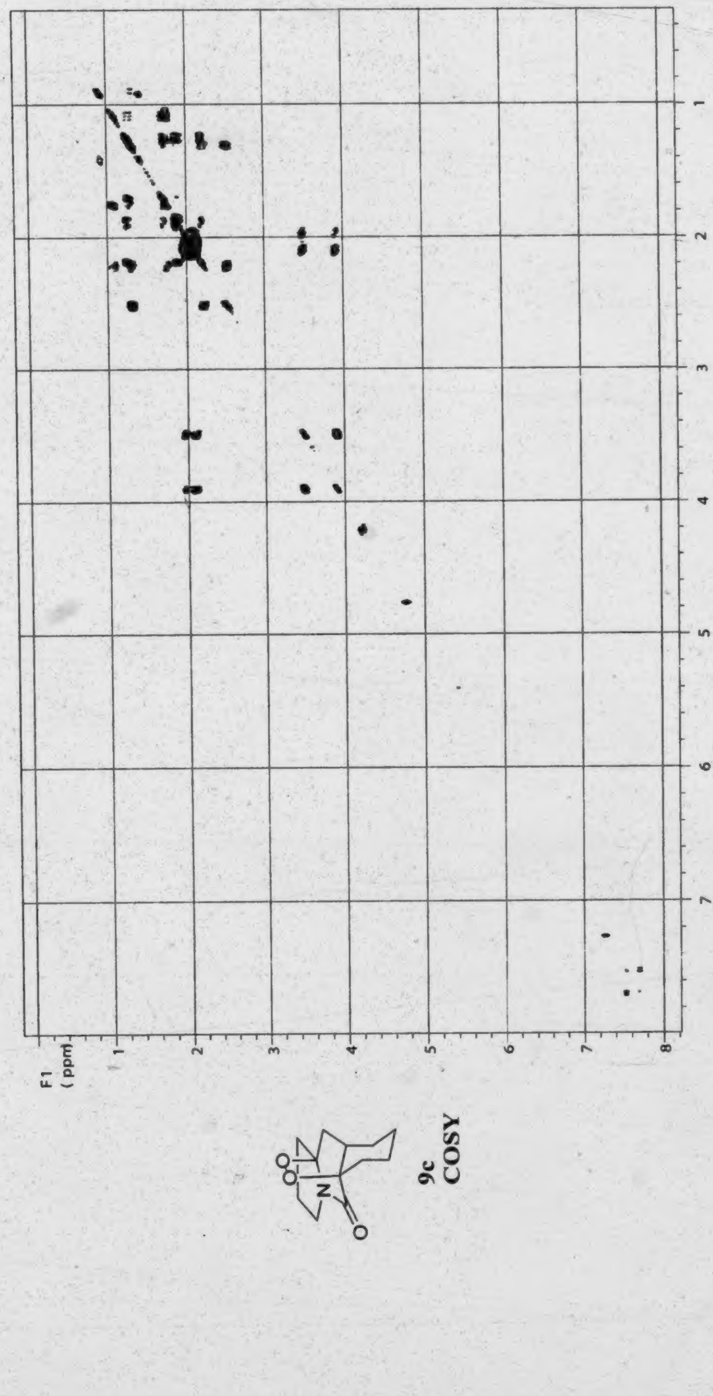
9b
HMBC

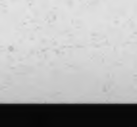

ppm
-0
1
2
3
4
5
6
7
8
9
10
5.54
5.43
5.79
27.5
2.37
18.06
5.57
11.3
3.81
5.54
N
O
O
O

9c

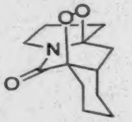


9c

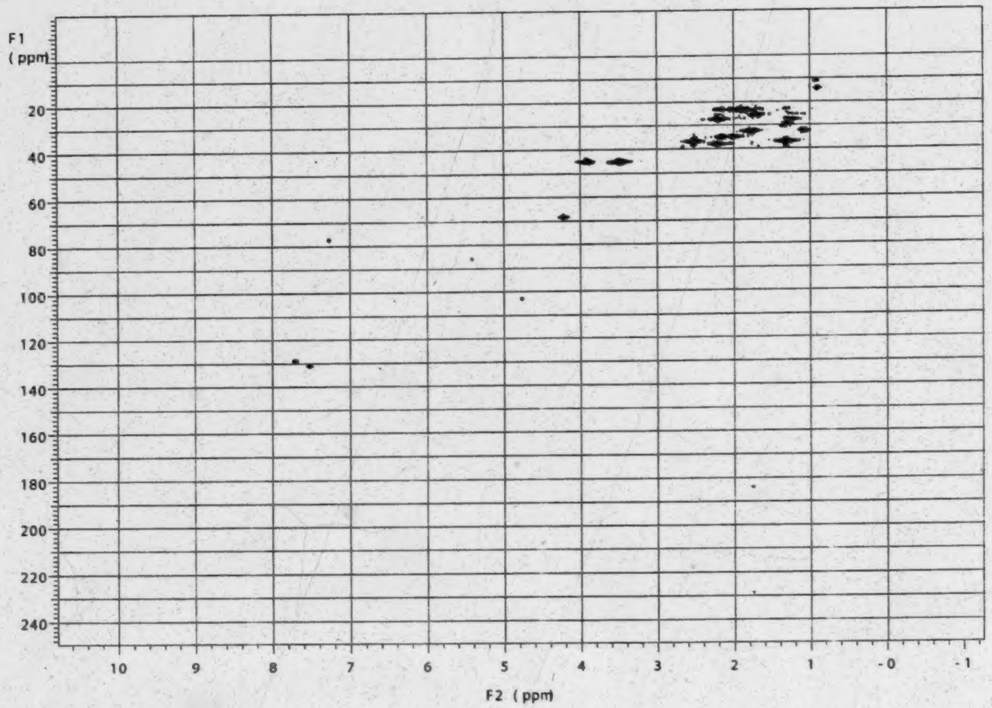


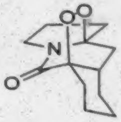


9c
COSY

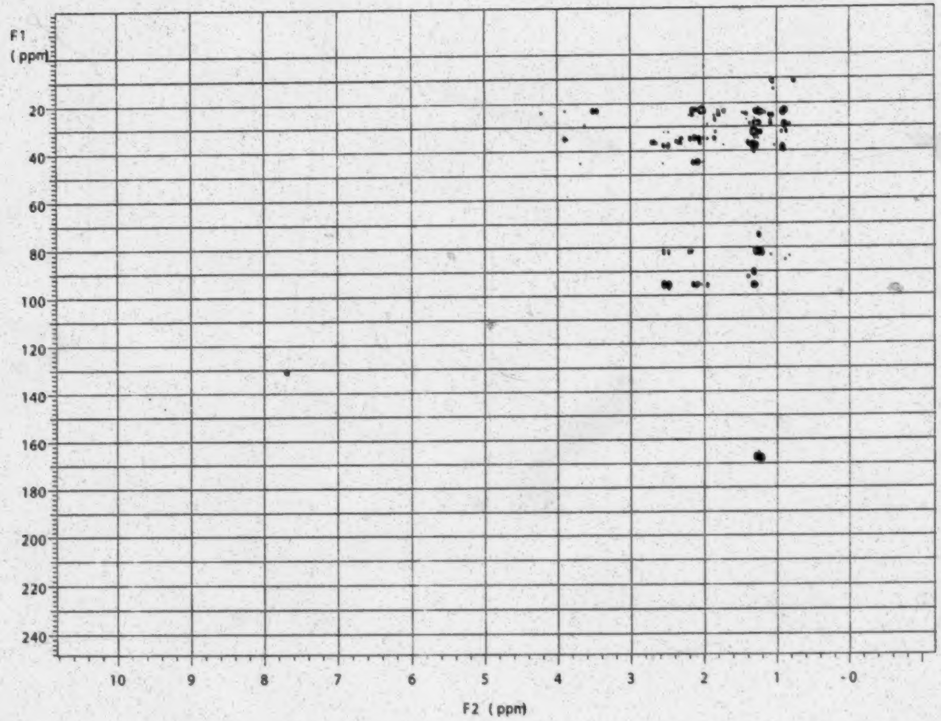


9c
HMQC


F1
(ppm)
20
40
60
80
100
120
140
160
180
200
220
240
10
9
8
7
6
5
4
3
2
1
-0
-1
F2 (ppm)


O
O
N
O

9c
HMBC


F1
(ppm)
20
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80
100
120
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200
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240
10
9
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7
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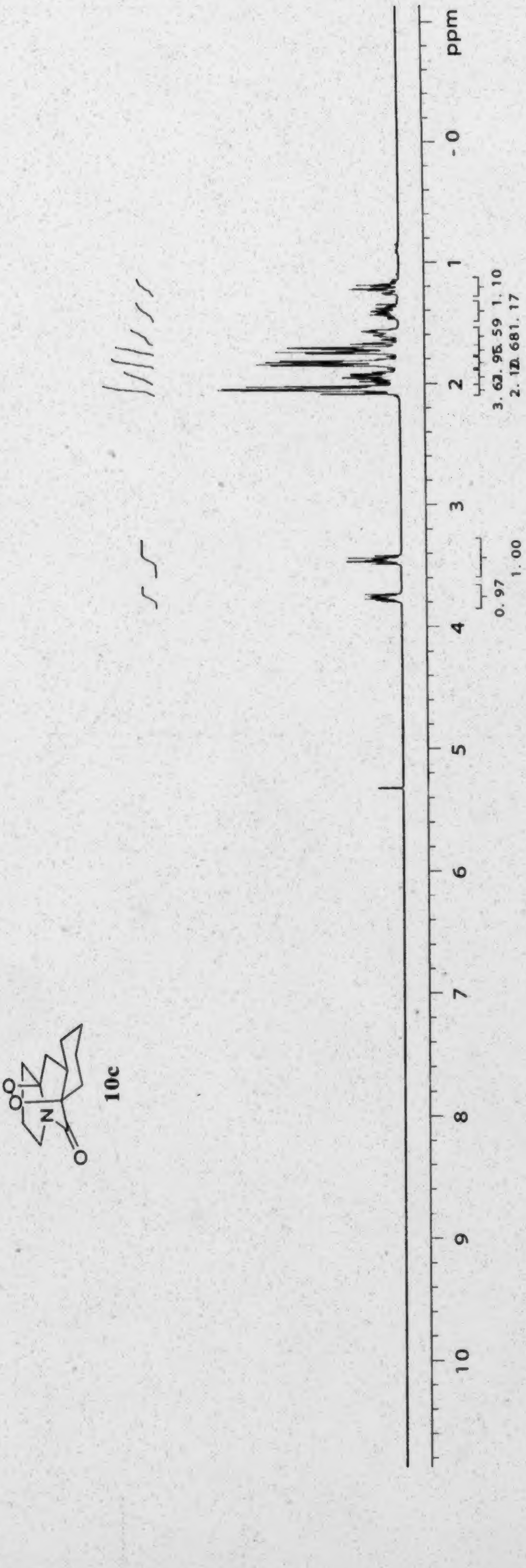
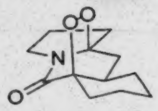
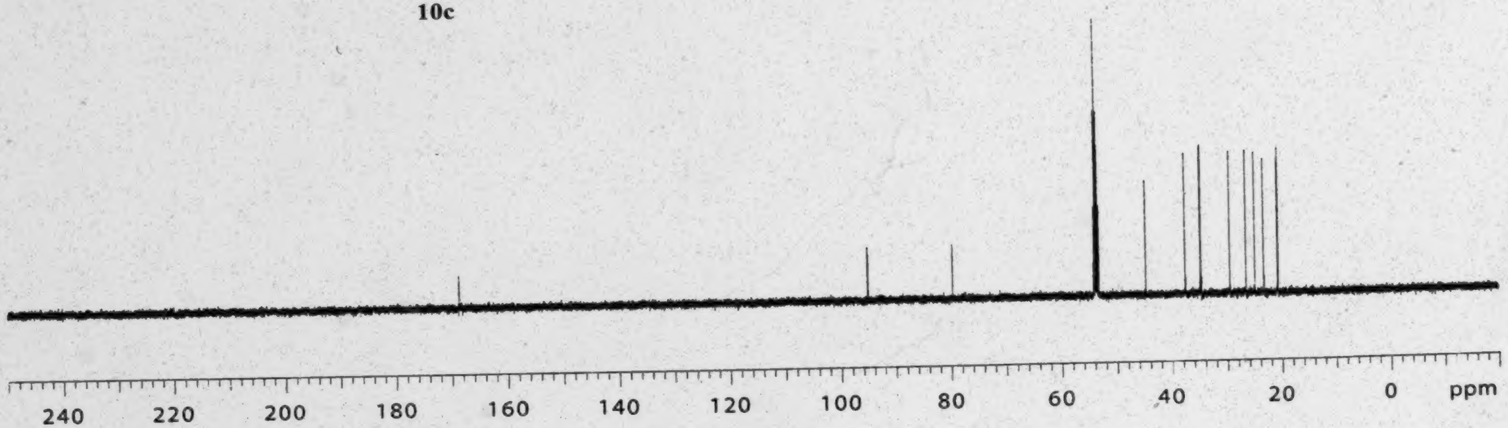
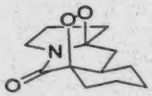
5
4
3
2
1
-0
F2 (ppm)


10c

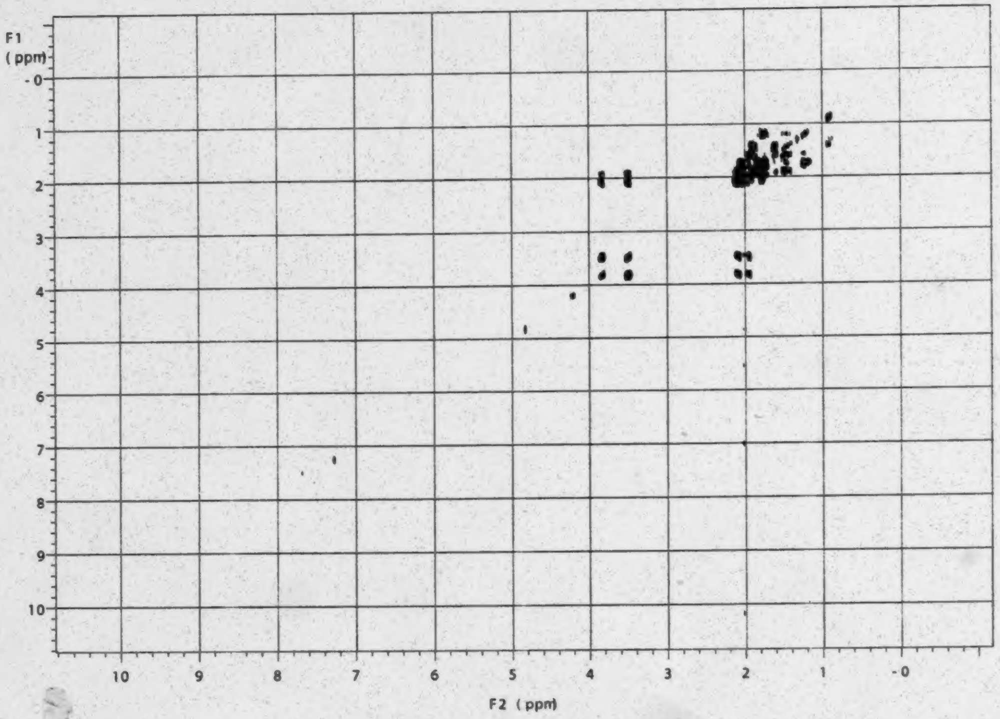


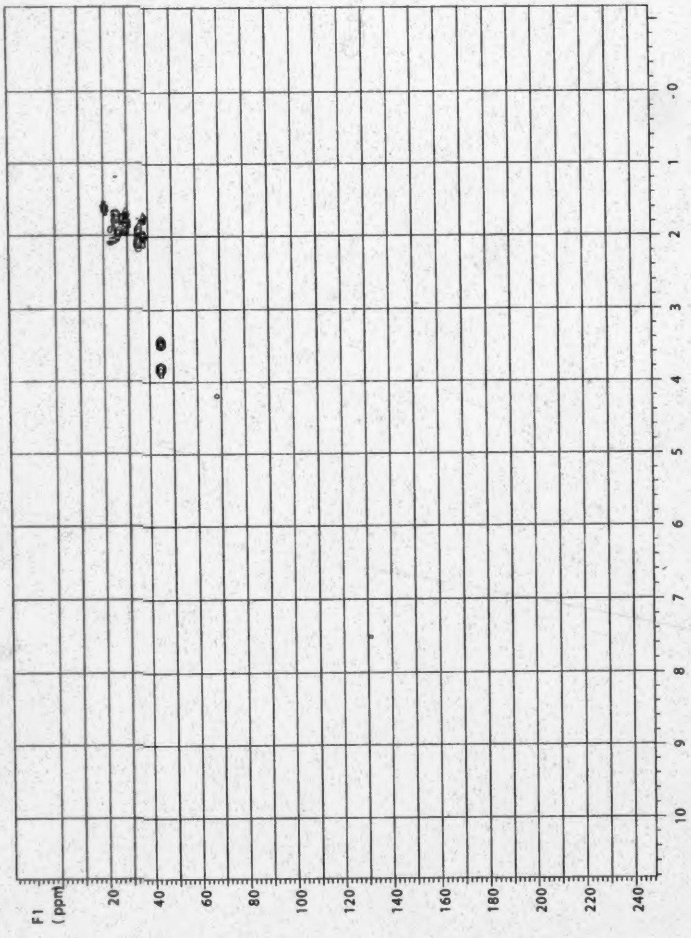
10c

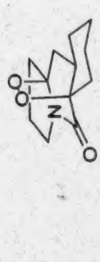




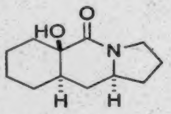
10c
COSY



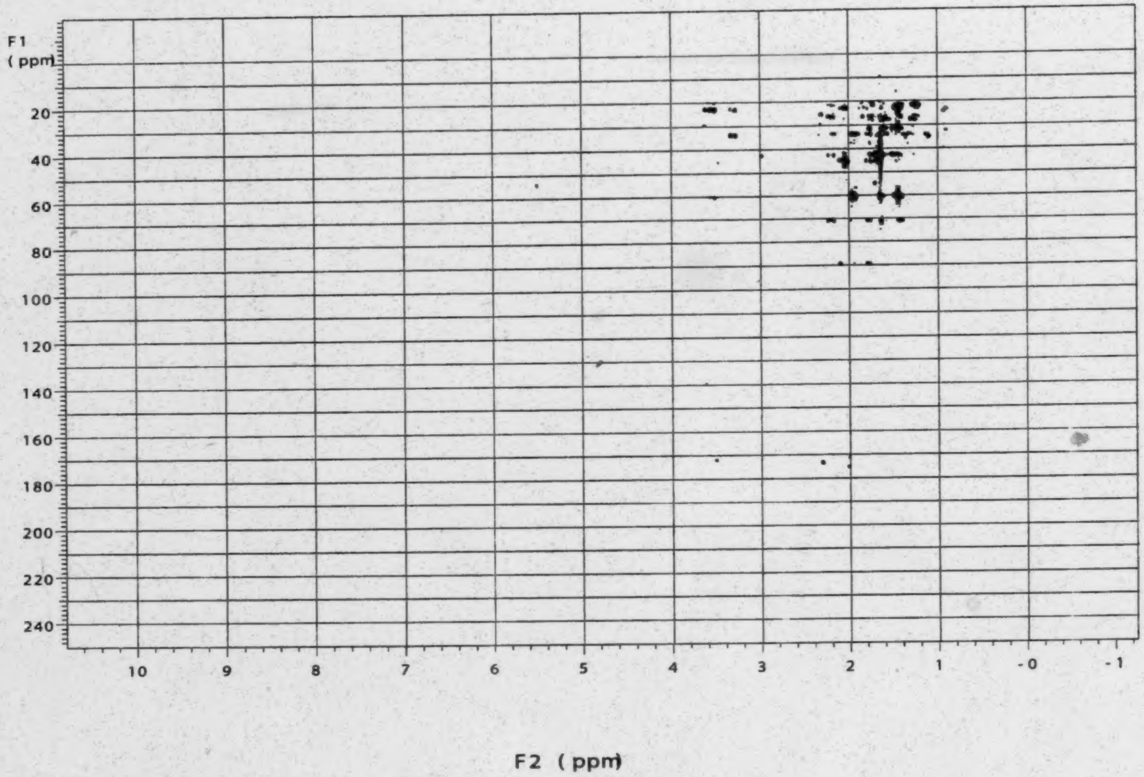

F1
(ppm)
20
40
60
80
100
120
140
160
180
200
220
240
-0
1
2
3
4
5
6
7
8
9
10
F2 (ppm)

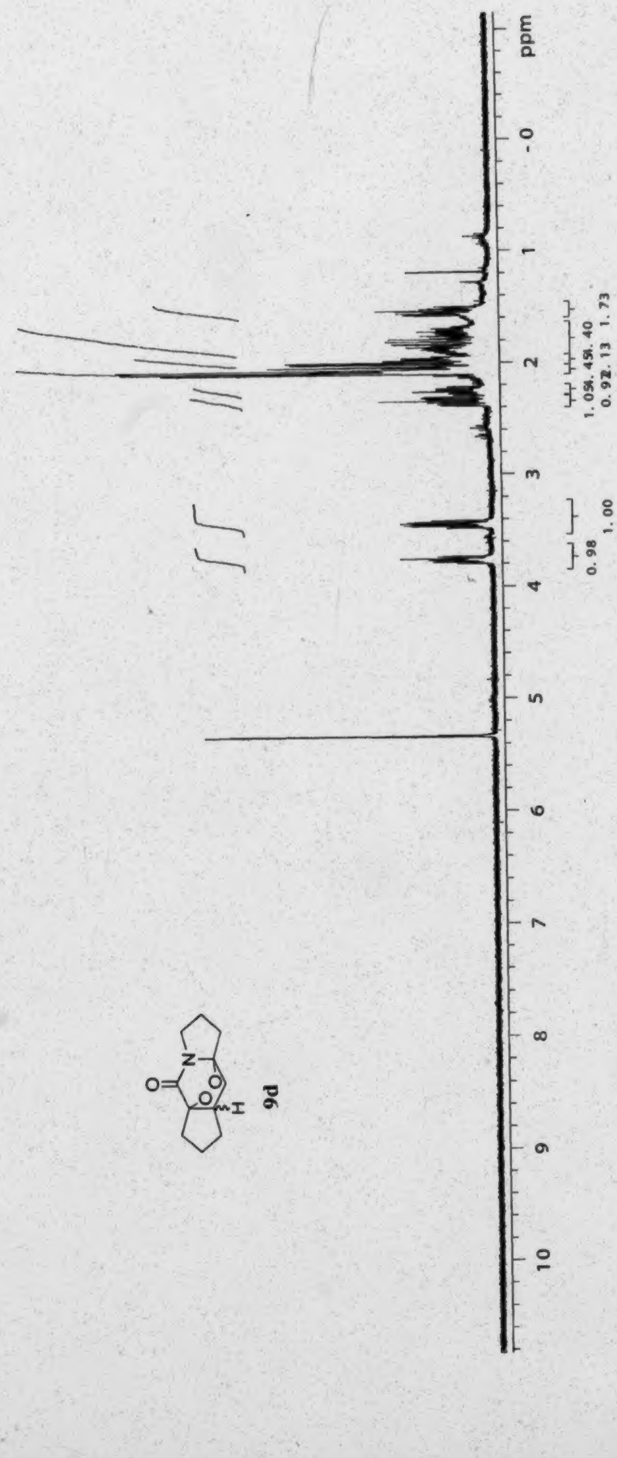

O
O
N
O

10c
HMQC

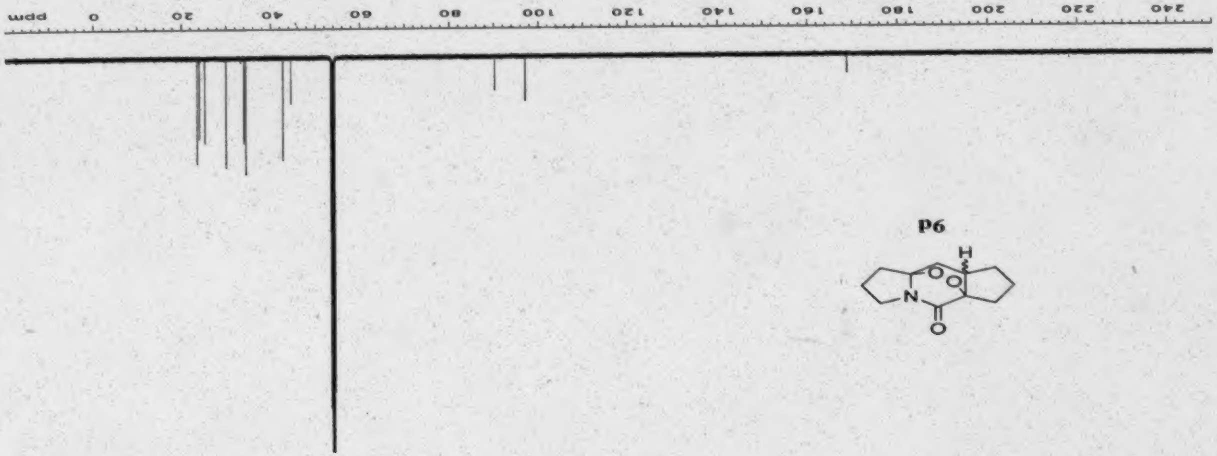

HO
O
N
H
H

12c
HMBC

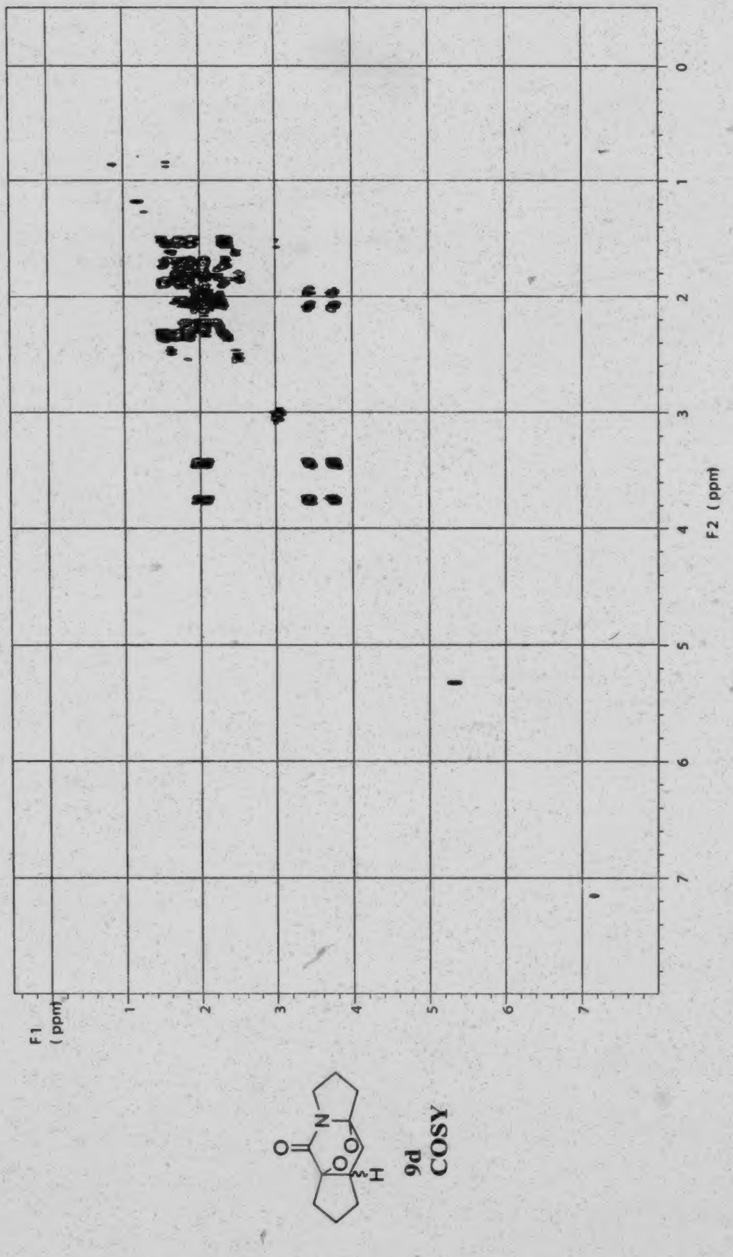

F1
(ppm)
20
40
60
80
100
120
140
160
180
200
220
240
10
9
8
7
6
5
4
3
2
1
-0
-1
F2 (ppm)



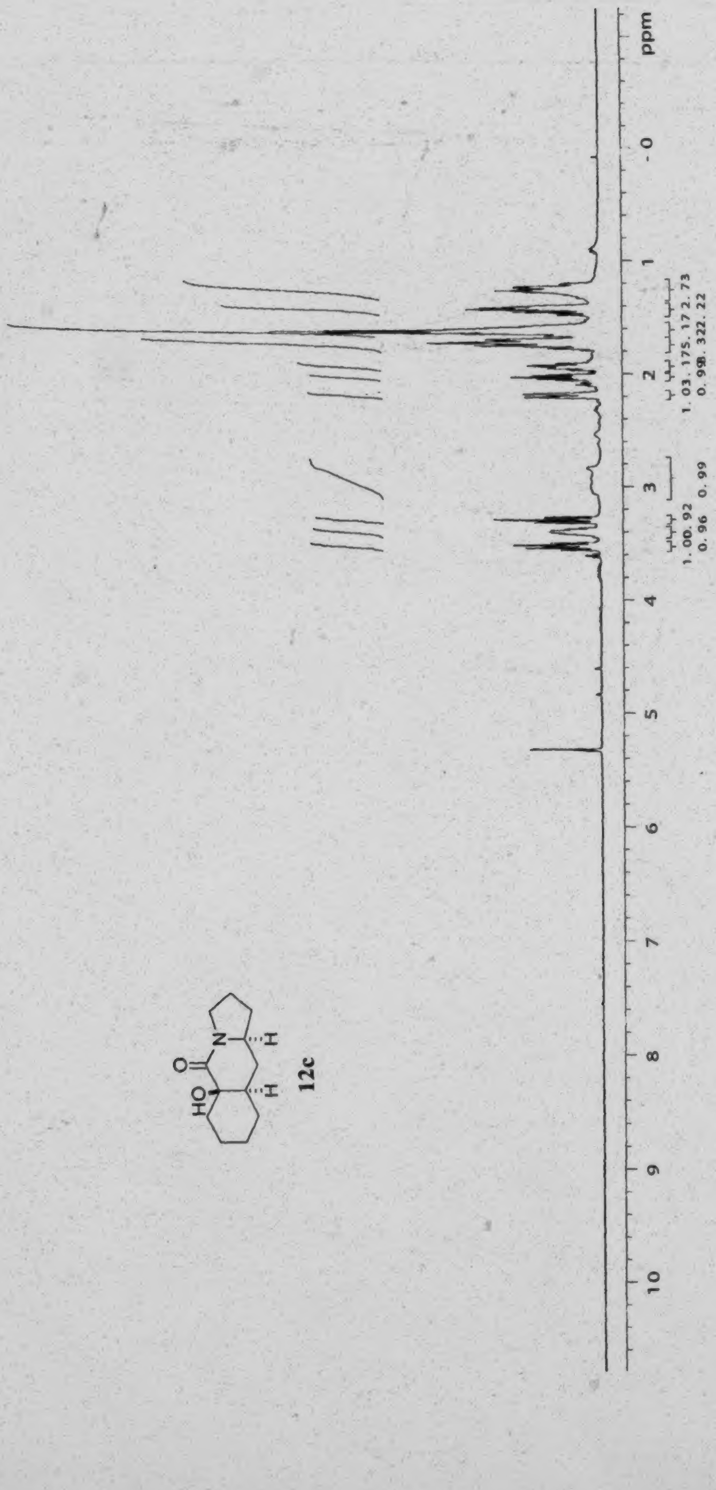
9d



P6

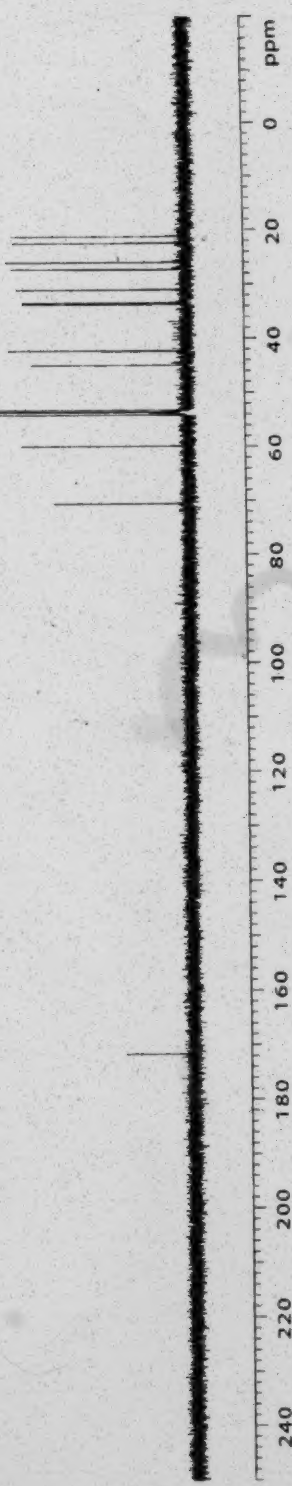


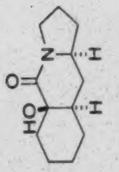
9d
COSY



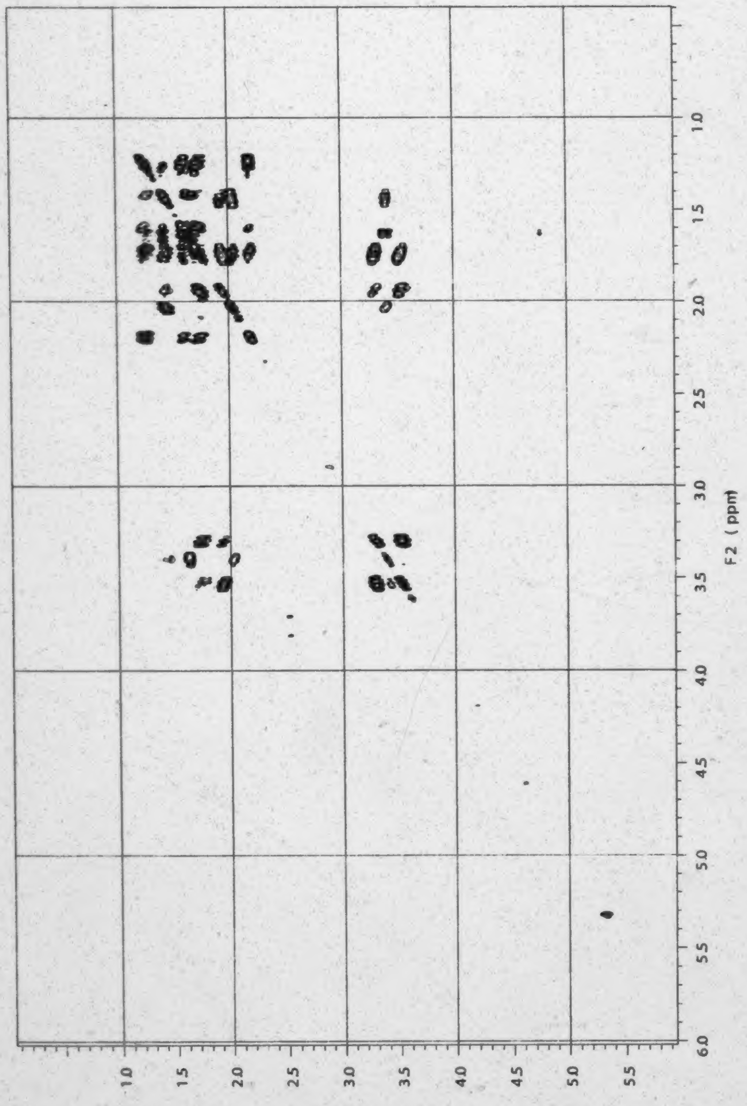
12c

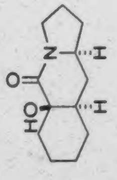
HO
O
N
H
H
ppm
10
9
8
7
6
5
4
3
2
1
0
1.00.92
0.96
0.99
1.03.175.172.73
0.99.322.22



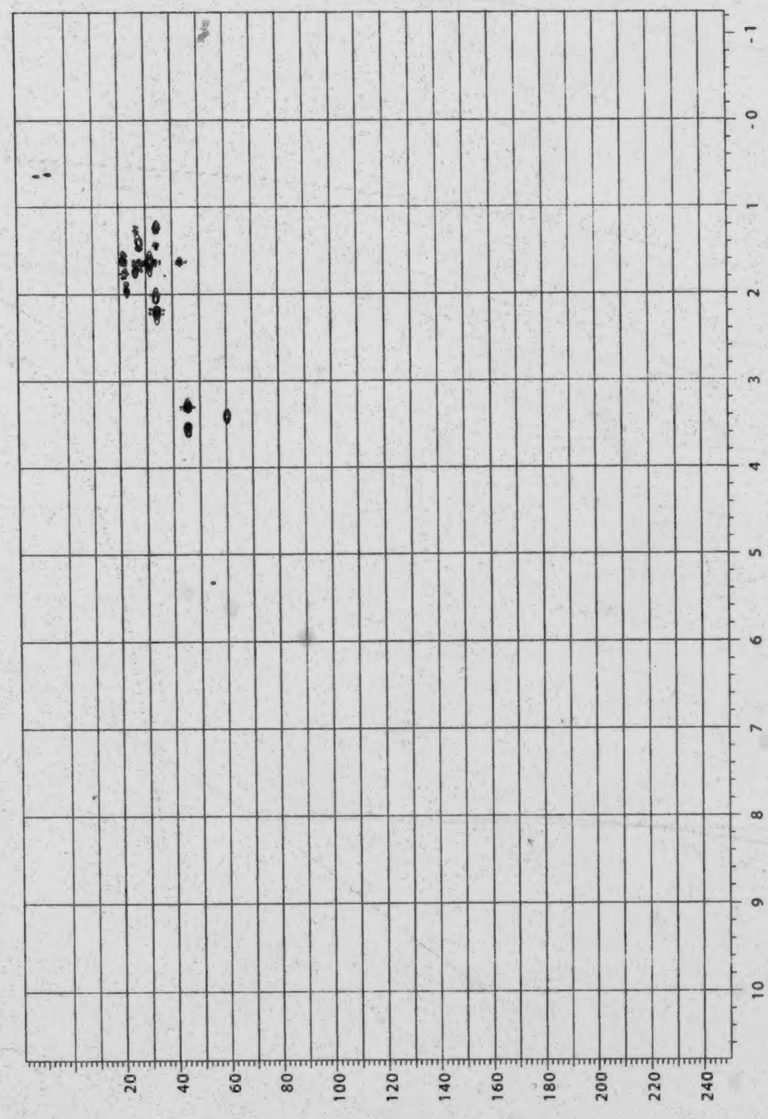


12c





12c


F2 (ppm)
-1
-0
1
2
3
4
5
6
7
8
9
10
20
40
60
80
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120
140
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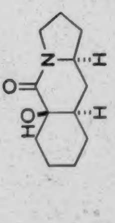
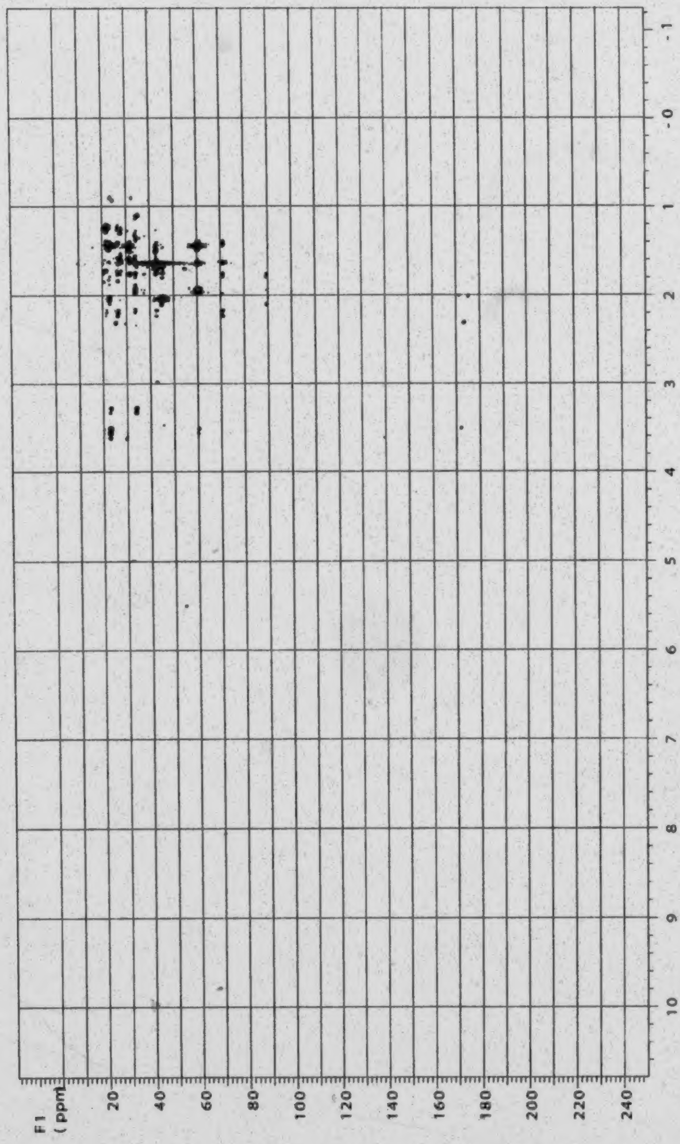
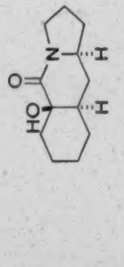
180
200
220
240

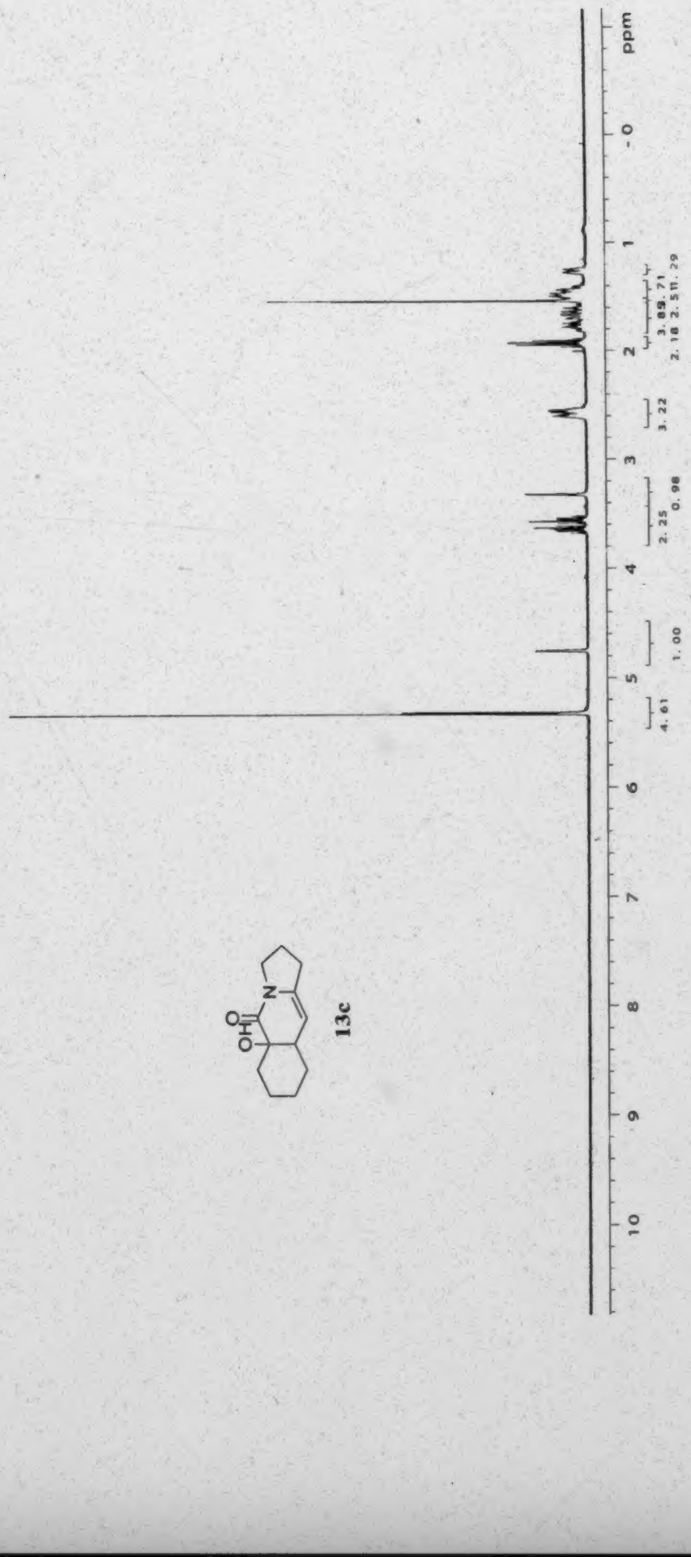

O
N
HO
H
H

12c
HMQC


F2 (ppm)
10
9
8
7
6
5
4
3
2
1
-0
-1
F1 (ppm)
20
40
60
80
100
120
140
160
180
200
220
240


HO
O
N
H
H

12c
HMBC



13c

13c